MANAGING HIV TREATMENT IN RESOURCE-LIMITED AND DYNAMIC ENVIRONMENTS

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Containing the HIV epidemic is one of the most pressing global health care issues. Antiretroviral therapy, the only treatment option for chronic HIV, inhibits the progression of the disease. However, there is a severe shortage of treatment in the developing world, particularly in Sub-Saharan Africa, the area hit the hardest by the epidemic. The current guidelines recommend treating HIV patients until death, known as a nonabandonment policy. HIV-infected patients develop resistant mutations and they benefit marginally from treatment. Therefore, there is an opportunity cost for treating patients until they die. We estimate the price of nonabandonment policies in HIV treatment where resources are limited. We develop a mathematical framework to optimize the allocation of scarce HIV treatment for a broad class of admissible policies. Pursuant to this goal, we develop a Markov model of the progression of a population of susceptible and infected individuals. Then, we restrict our attention to two classes of admissible policies: (i) nonabandonment policies, and (ii) abandonment-permitted policies. The price of nonabandonment policies is estimated by the difference between the optimal solution of these two classes of admissible policies. Since the state spaces of the models are unbounded, solving the allocation problems is intractable. Therefore, we approximate the price of nonabandonment policies by the difference between a lower bound on the best performance of allocation policies in abandonment-permitted settings and an upper bound of that in nonabandonment settings. We show that the price of following the nonabandonment policies in HIV treatment is as much as 41%. Moreover, they shed light on the key role allocation policies play in containing the epidemic. In resource-

rich environments, when to start HIV treatment is a fundamental question. Current models do not consider the rate of new antiretroviral development in their analysis. We model the arrival of HIV pipeline drugs in resource-rich environments as a split Poisson process and incorporate it in a validated simulation model to measure the effect of HIV pipeline drugs on HIV treatment. The model with the inclusion of pipeline drugs recommends earlier treatment.

Keywords: HIV, Resource-Limited Settings, Nonabandonment, Approximate Dynamic Programming, Split Poisson Process, Pipeline Drugs.

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PREFACE

To Fattaneh and Yadollah

1.0 INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition that progressively reduces the effectiveness of the immune system. HIV/AIDS has infected 34 million people worldwide and killed over 20 million since 1989 [WHO, 2010]. In 2010, 2.7 million people became infected with HIV and 1.8 million people died of AIDS-related causes [Joint United Nations Programme on HIV/AIDS, 2010].

CD4 cells, a type of white blood cell, protect the human body from infection. HIV attacks CD4 cells and kills them. As CD4 cells become depleted, HIV patients become more vulnerable to infectious diseases, resulting in AIDS and eventually death [Stine, 2003]. Antiretroviral therapy (ART), the only treatment option for chronic HIV infection, is capable of effectively regulating the progression of the virus. The first ART, known as AZT, was introduced in 1986 [Shernoff and Smith, 2001]. Due to developing resistant mutations, the effect of AZT on patients' health becomes limited [Shernoff and Smith, 2001]. Therefore, by developing new drugs, treatment of HIV has changed to highly active antiretroviral therapy (HAART). HAART involves taking a combination of antiretroviral (ARV) drugs which usually entails three drugs from various classes [United States Department of Health and Services, 2004]. HAART has significantly decreased the HIV mortality rate, and the status of HIV has been transformed from a fatal disease to a chronic one [Palella Jr. et al., 1998].

While treatment options are largely available in the developed world, access to ART remains one of the biggest public health problems in the developing world, where demand for treatment largely exceeds its supply [WHO, 2010]. For instance, in Sub-Saharan Africa, more than 22 million people are infected and coverage[1] in this area ranges from 23% in Niger

[1]Coverage is defined as the number of patients treated divided by the total number of patients.

to 83% in Botswana, with the majority of countries having coverage less than 40% [Joint United Nations Programme on HIV/AIDS, 2010]. As a result, in 2010, ten million patients in need of treatment did not receive it [Joint United Nations Programme on HIV/AIDS, 2010]. While the number of ART doses available to patients has steadily risen over the course of the last 20 years, the number of HIV cases has also continued to increase [WHO, 2010]. Looking ahead, current funding for HIV international programs is well below the funding level required to contain the epidemic: while the latter is expected to grow by $2 billion in 2015, the former, currently $3-4 billion below current needs, remains virtually constant [UNAIDS, 2012].

The focus of this dissertation is on two problems in HIV treatment. In Chapter 3, we develop a simulation model to investigate the social effects of ART on containing the HIV epidemic in resource-limited settings. The HIV progression of an infected individual in the population is governed by a validated microsimulation model. To capture limited resources, we consider a limited number of treatment doses. Treatment increases the size of the infected population because treated patients live much longer than untreated ones. We investigate the effect of treatment on the population size at different coverage levels. We also show that the current definition of coverage by WHO falls short of fully describing the effects of HIV treatment on the population. We provide a new definition for coverage that describes the effect of ART on population size more precisely. We show that current published coverage data, which indicates that the HIV epidemic in Africa is nearly half-way to being fully treated, does not consider the dynamic effects of coverage on the size of the infected population.

International guidelines recommend treating HIV-infected patients until they die, known as nonabandonment policies. HIV-infected patients develop resistant mutations to treatment and marginally benefit from it. Following a nonabandonment strategy hinders policy makers from reallocating available treatment doses to other patients who might benefit more. Therefore, the whole population is affected by an opportunity cost by keeping patients on treatment until death. In Chapter 4, we introduce a mathematical model to quantify the price of nonabandonment policies in HIV treatment when resources are limited. First, we propose a mathematical framework for optimizing the allocation of scarce HIV treatment doses in a

heterogeneous population for a broad class of admissible policies. Then, we restrict our attention to two classes of nonabandonment and abandonment-permitted admissible policies. We define the price of nonabandonment as the difference between the solutions of abandonment-permitted and nonabandonment. Due to an unbounded state space, solving these problems is intractable. Therefore, we estimate a lower bound on price by the difference between a lower bound on improvement for the abandonment-permitted setting and an upper bound on improvement in the nonabandonment setting. We use the linear programming approach to approximate dynamic programming (ADP) to find efficient solutions and derive structural properties of the proposed policies. Moreover, by providing upper bounds, we show that the policies produced by our approximation method are close to optimal. In particular, the price of nonabandonment is as much as 41% of the total discounted life expectancy of the whole population. We use clinically validated HIV progression and transmission models to calibrate our model and evaluate the performance of policies produced by approximate dynamic programming. We compare these policies against the recommendations of the World Health Organization (WHO). Our results indicate that the proposed policies outperform WHO recommendations in terms of total discounted quality-adjusted life-years (QALYs) of the population by as much as 8%. Moreover, they shed light on the key role allocation policies play in containing the epidemic.

Additionally, the question of when to initiate HIV treatment in resource-rich environments has received significant attention. On one hand, early treatment reduces the viral load in early stages of infection and, therefore, decreases the likelihood of irreparable damage to the immune system. On the other hand, early treatment increases the likelihood of developing resistant mutations and adverse effects of HIV treatment due to toxicity. All of the available models consider a fixed number of HIV therapies in analyzing the optimal time to initiate HIV treatment. In Chapter 5, we investigate the effect of the rate of new antiretroviral drug development on HIV treatment and in particular, on the optimal time to initiate the therapy. We model the arrival of pipeline drugs as a split Poisson process and incorporate it into the previously validated simulation model. Including pipeline drugs in the model supports early treatment in almost all cases. In addition, the predicted life expectancy gains with the presence of pipeline drugs range from almost nothing to 8%, depending upon the

age of patients, viral load, and the CD4 count at which therapy is initiated. Our results show that the most important factor in increasing the quality-adjusted life-years due to pipeline drugs is reducing the toxicity.

We discuss conclusions, limitations, and future extensions of the dissertation in Chapter 6.

2.0 LITERATURE REVIEW

Because the literature on HIV is extremely broad, we focus only on the literature that is related to this dissertation. First, we provide a brief medical literature review on treatment initiation times in resource-rich settings. Next, we provide a brief literature review on mathematical and simulation models used for analyzing when to start treatment, analyzing HIV transmission dynamics, and analyzing the effect of treatment on transmission. Finally, we describe an overview of the HIV simulation model used in to develop our simulation models.

2.1 CLINICAL STUDIES

Since the discovery of HIV, researchers have debated when patients should initiate therapy [Lepri et al., 2001]. After an initial phase, where early initiation was recommended, it soon became apparent that early initiation resulted in a multitude of side effects and early acquisition of resistant mutations [Sulkowski et al., 2000]. In this regard, Phillips et al. [2003] recommend late treatment initiation so as to balance the trade-off between immune system recovery and the cumulative effect of drug toxicity. Sterling et al. [2003] show that patients who wait for starting treatment until their CD4 count drops below 350 cells/mm^3 have the longest survival. Siegfried et al. [2010] report the results of many randomized controlled trials that consider the optimal time to initiate HIV treatment. Lawn et al. [2011] have a literature review of clinical trials for the optimal time to initiate HIV therapy in patients with HIV-associated opportunistic infections.

2.2 MATHEMATICAL AND SIMULATION MODELS

Researchers have used mathematical models to determine the optimal time to initiate HIV treatment. Badri et al. [2006] consider a Markov state-transition model to estimate the life expectancy and the treatment cost for several treatment initiation policies. Braithwaite et al. [2008] develop a simulation model to investigate the optimal threshold for HIV treatment initiation. Shechter et al. [2008] model the problem of when to initiate therapy as an optimal stopping problem using Markov decision processes.

The availability of different ART regimes[1] in resource-rich environments has brought attention to the issue of ART sequencing and optimization. In this context, Wein et al. [1997] cast optimal individual ART treatment using control theory. There, a decision maker attempts to control a patient's viral load[2] (VL) by suggesting dynamic therapies; see, for example, Kirschner et al. [1997], Brandt and Chen [2001], and Jeffrey et al. [2003] for similar approaches. To the best of our knowledge, all of these studies deal with the issue of ART for a single patient and implicitly assume drugs are available to patients whenever they wish to initiate or switch treatment regimens. In our study, drug availability is restricted and, to some extent, endogenously determined, as is treatment initiation.

In addition to the "when to start treatment" problem, many researchers have tried to investigate the effect of treatment on HIV transmission. In particular, societal approaches to treatment allocation have received significant attention in recent decades, mostly from the clinical literature. Central to such an approach is a model of transmission dynamics, which plays a major role in the study of the evolution and control of related sexually transmitted diseases (STDs); see, for example, Mollison [1995], Anderson and May [1991], Watts and May [1992], and Kretzschmar and Morris [1996]. Our modeling effort follows closely that of Garnett and Anderson [1994] who model the sexual behavior of a population via a system of differential equations. As in our model, they consider different risk groups, shaped according to their sexual behavior, and an exogenous mixing pattern in the population.

[1] The ART regimen is a combination of antiretroviral medications.
[2] Viral load estimates the amount of virus in a mL of blood.

ART effect on the progression of the HIV epidemic remains unclear; see, for example, Wagner et al. [2010], and Velasco-Hernandez et al. [2002]. In this regard, the work of Baggaley et al. [2005] constitutes a first step in clarifying this issue. They review mathematical models which discuss the effect of HIV treatment in resource-limited settings. Blower et al. [2003] use a mathematical model to predict the effect of low or moderate rate of ART usage on HIV prevalence and incidence in the developing world. Granich et al. [2009] develop a mathematical model to predict the effect of widespread use of ART and especially "screen and treat" strategy on the HIV epidemic. They show that by implementing the screen and treat strategy HIV will be eliminated in 50 years. However, Wagner et al. [2010] argue that the model used in Granich et al. [2009] does not consider the development of resistant mutations and does not consider the effect of ART on the population size.

It is worth noting that none of the studies above consider the effect of allocation policies on the HIV epidemic. An exception is the work by Walensky et al. [2009], who study HIV treatment in resource-limited settings. They explore the effect of different initiation policies on the life expectancy and the cost of treatment of patients at an individual level. Their results suggest the earlier treatment is more cost-effective, however, they do not model the drug scarcity constraints explicitly, and instead use a decision tree to predict patients' survival, conditioned on the results of a large control trial.

Zaric and Brandeau [2001] consider the problem of allocating resources to a limited number of *interventions*, such as needle exchange programs and condom use, to improve QALYs and the number of HIV infections averted. However, their model does not consider ART, a key HIV intervention. Restricting attention to a limited set of allocation policies, the authors show that the efficiency of a policy depends on factors such as incidence and prevalence, and which interventions are considered. Long et al. [2006] explore an epidemic model of HIV in a population of injection drug users (IDUs) and non-IDUs. They investigate the cost-effectiveness of ART in the population.

There has been recent interest in applying ADP to health care problems. Maxwell et al. [2009] model the problem of efficient ambulance redeployment and use simulation to tune the parameters of their value function approximation. Patrick et al. [2008] explore a dynamic multi-priority scheduling model for patients in a diagnostic facility. They use the linear

programming approach to ADP to minimize patient waiting time. Erdelyi and Topaloglu [2009] study a similar problem using ADP in policy space by parameterizing protection-level based policies. Lee et al. [2008] examine the problem of optimal timing and management of dialysis therapy. They develop an ADP algorithm to maximize a patient's welfare and use a simulation model to derive near-optimal strategies. Our work uses ADP methods to craft efficient treatment allocation policies.

Computing upper bounds in stochastic dynamic programming is a vexing problem. Brown et al. [2010] provide a technique to compute an upper bound for a finite-horizon stochastic dynamic program by relaxing information and using duality. For using this approach one needs to generate sample paths of the original problem, find a good penalty function, and solve the deterministic dynamic program. However, in our model in Chapter 4, generating a sample path for the whole population for a finite horizon is burdensome. Moreover, solving the deterministic dynamic program is extremely challenging since there is exponential number of ways to allocate treatment at each step. In addition, the quality of upper bounds depends on the choice of the penalty function. We provide two techniques to compute upper bounds to guarantee the quality of our approximations.

2.3 OVERVIEW OF INDIVIDUAL HIV SIMULATION MODEL

The HIV simulation model in Chapter 3 is based on an individual microsimulation model that replicates the probabilistic progression of the disease in a patient over time [Braithwaite et al., 2011]. The model tracks the health of a patient on a daily basis: viral load updates consider the history of resistant mutation and compliance, and CD4 count updates consider several factors such as VL, treatment status, and age; it also replicates the progression of resistant mutation biologically. The development, mechanics, and validation of this model have been previously described [Braithwaite et al., 2006, 2007]. The simulation model computes HIV-mortality rates based on health and age of a patient, and non HIV-mortality rates based on age and the drugs' toxicity and side effects.

The model, originally calibrated and validated on data in the US, has demonstrated the ability to predict time to treatment failure [Braithwaite et al., 2005], the development of resistant mutations [Braithwaite et al., 2006], survival, and change in CD4 count and viral load over time [Braithwaite et al., 2008], both with and without treatment. Recently, a version of the model calibrated with data from western Kenya has been used to test alternative thresholds for treatment initiation and the effect of adherence on the quality-adjusted life-years for patients in Sub-Saharan Africa [Braithwaite et al., 2011]. We extend this version of the model to conduct our dynamic simulations.

3.0 A SIMULATION MODEL OF HIV TREATMENT IN RESOURCE-LIMITED SETTINGS

3.1 INTRODUCTION

The development of highly active antiretroviral therapy has revolutionized the treatment of HIV disease, producing dramatic increases in survival [Palella et al., 2003]. However, the benefits of these therapies have not been fully realized in many resource-limited environments. The lack of sufficient treatment has been especially severe in Sub-Saharan Africa, where many countries are able to provide HIV treatment to only a small portion of the population infected with HIV. The screen and treat strategy recommends treating HIV-infected individuals regardless of their CD4 count [Wagner et al., 2010]. Researchers disagree about implementing the screen and treat strategy, especially in resource-limited settings. For instance, Granich et al. [2009] show that the HIV epidemic can be eliminated by using the screen and treat strategy and recommend widespread use of this strategy. However, this model does not consider the effect of developing resistant mutations and the effect of ART in increasing the life expectancy of HIV-infected patients. Moreover, there is a debate about whether the screen and treat strategy is implementable in resource-limited settings [Dodd et al., 2010].

Over the past decade, cooperation between developed nations, the pharmaceutical industry, the World Health Organization and many private charities has resulted in a dramatic increase in the resources available to resource-limited nations to treat HIV disease. A common measure of the success of these efforts is the increase in "coverage"; the proportion of HIV-infected population meeting criteria for treatment who are being treated. In 2010, the coverage levels in most Sub-Saharan African countries was less than 40%, leaving large

portions of the population untreated. However, in just a few years, international efforts have increased coverage rates substantially. In Sub-Saharan Africa, the average coverage level has increased form 3% in 2003 to 49% in 2012 [WHO, 2012].

One direct consequence of expanded access to treatment is a growth in the size of the HIV-infected population who qualify for treatment. Because patients on therapy live substantially longer than patients without therapy [Palella Jr. et al., 1998], treatment will increase the size of the HIV-infected population who qualify for treatment, and therefore increase the resources required to fully treat that population. The purpose of this chapter is to estimate the impact of various levels of treatment coverage on the resulting size of the HIV-infected population who qualify for treatment.

3.2 SIMULATION MODEL

We adapted an existing, validated individual simulation model of HIV, calibrated on data from Sub-Saharan Africa [Braithwaite et al., 2011] that predicts the progression of HIV on and off treatment to represent a dynamic population of HIV-infected patients under various assumptions regarding the number of doses of antiretroviral therapy available. The population is dynamic in that we represent new infections being added to the cohort at a constant rate. To illustrate the problem, we consider the situation in which only a single ARV regimen is available and analyze the relationship between the resources available for HIV treatment and the resulting size of the stable HIV-infected population. This assumption is quite mild in this setting because second line and third line therapies are much more expensive and their efficacy is not significantly higher [Pujades-Rodriguez et al., 2008].

3.2.1 Overview of Population HIV Model

We extend the Braithwaite et al. [2011] individual HIV model by running multiple unique copies of the model simultaneously to represent a cohort of patients and to simulate the effect of different levels of scarce ART doses. We create an initially stable HIV-infected

population of an arbitrary size, setting the new HIV-infection rate equal to the death rate of the HIV-infected population in the absence of treatment. When patients are treated, the population size grows over time because treated patients live longer than untreated patients, resulting in a death rate lower than the new HIV infection rate. The population continues to rise until the number of deaths once again equals the new infection rate, at which time a new stable population size is reached. We identify the effect of treatment on the stable population size, and estimate the resource required (as represented by the number of doses of ART) to treat the entire population.

We assume that in the beginning of the simulation there is a set number of doses of first line ARV available. As there are insufficient doses to treat everyone, the model chooses which patients to start on therapy using the World Health Organization recommendations for resource-limited settings, which prioritizes therapy initiation for the sickest patients (patients with the lowest CD4 count), and keeps patients on treatment until they die [WHO, 2012]. That is, a dose of ART becomes available only when a patient on therapy dies.

3.2.2 Definition of Coverage

The size of the HIV-infected population will change over time depending on the amount of ART available. When not everyone in the population can be treated, some HIV-infected patients will acquire HIV disease, become ill and die without receiving ART. Therefore, we define two coverage concepts: (i) *prevalence-based coverage*, which refers to the number of doses divided by the HIV-infected population at a given time; and (ii) *cumulative incidence-based coverage*, which refers to the number of patients who receive treatment at some point during their life. One might interpret the prevalence-based coverage as the perceived coverage and the cumulative incidence-based coverage as effective coverage.

Example 1 *We illustrate these definitions and their differences by means of a simple example: suppose that*

- *untreated patients live exactly 2 years;*
- *treated patients live exactly 14 years;*
- *only 1 ARV dose is available;*
- *the new HIV infection rate is equal to the death rate from HIV disease (a new case develops every 2 years).*

Figure 1 illustrates this scenario: at any given time, prevalence-based coverage is 50% as one half of the current HIV-infected population is being treated, but over a 14-year period only one of a total of eight HIV-infected individuals receives treatment for a cumulative incidence-based coverage of 12.5%.

The common interpretation of coverage (which we call prevalence-based coverage), is a "snapshot" measure, and overestimates the number of HIV-infected individuals who receive treatment, as at most levels of coverage, many eligible HIV-infected patients will acquire HIV, live through their progressive disease and die prior to receiving ART. We consider an initial

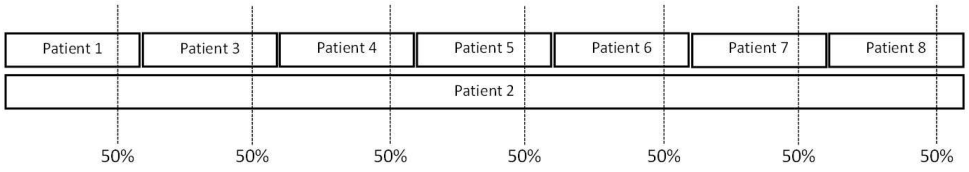


Figure 1: Prevalence-based and cumulative incidence-based coverage

population of 10,000 HIV-infected patients and vary the number of doses available from zero until everyone who qualifies for coverage is able to receive treatment. After an increase in the number of ART doses available, the HIV-infected population rises, and stabilizes at a higher steady state. The warm-up period takes around 20 years, after which the infected population size stabilizes. Simulations are run for 300 years after reaching steady state to provide stable estimates of the prevalence-based and cumulative incidence-based coverage,

and the population size at that number of available doses. In addition, we relate the stable population size and cumulative incidence-based coverage to the portion of people currently living at various levels of prevalence-based coverage in Sub-Saharan Africa.

3.3 A QUEUEING MODEL

We use queueing theory to model the population of HIV-infected patients and derive expressions for the prevalence-based and cumulative incidence-based coverage, as well as the stable population size.

We consider a queueing system in which customers arrive from an infinite pool of population and d servers are available. An arriving customer is served immediately if there is a free server, and joins a single queue otherwise. We assume that the service times of customers are independent and have distribution G, and the arrival process of customers has inter-arrival distribution F. In our setting, patients are customers and treatment doses are servers. Because patients may die while waiting for treatment, we have a $G/G/d$ queueing system with reneging.

Suppose that we have a population of N_0 infected patients. In the base case, the expected number of patients who enter the system is equal to the expected number of patients who die. Note that we do not consider the physiological characteristics of infected individuals. In particular, we assume that the probability of death for a patient is independent of her health when she is waiting for treatment in the queue and when she has started treatment. Let P_n denote the n^{th} patient, and this patient enters the system at time t_n. The point process $\{t_n : n \geq 1\}$ is assumed to be an increasing sequence of nonnegative numbers with the counting process $\{N(t) : t \geq 0\}$. By this we have $N(t) = \max\{n : t_n \leq t\}$, where $N(t)$ shows the total number of patients who have entered the system by time t. Let W_n be the life-years of patient P_n after arriving to the system and t_n^d be the time when the patient dies. We have $t_n^d = t_n + W_n$. The departure process $\left\{N^d(t) : t \geq 0\right\}$ is the counting process for death times $\left\{t_n^d\right\}$, i.e., $N^d(t)$ shows the number of patients who died by time t. Note that almost surely $N^d(t) \leq N(t)$, $t \geq 0$. A patient is alive at time t if and only if

$t_n \leq t < t_n^d = t_n + W_n$. Let $L(t)$ be the total number of patients in the population at time t. We have

$$\begin{aligned} L(t) &= \sum_{n=1}^{\infty} I\left\{t_n \leq t < t_n^d\right\} \\ &= \sum_{n:t_n \leq t} I\left\{W_n > t - t_n\right\} \\ &= \sum_{n=1}^{N(t)} I\left\{W_n > t - t_n\right\}, \end{aligned}$$

where $I\{.\}$ is the indicator function. Let λ be the arrival rate to the system, ω be the average life-years, and ℓ be the time average number of patients. We have

$$\begin{aligned} \lambda &:= \lim_{t\to\infty} \frac{N(t)}{t}, \\ \omega &:= \lim_{n\to\infty} \frac{1}{n} \sum_{j=1}^{n} W_j, \\ \ell &:= \lim_{t\to\infty} \frac{1}{t} \int_0^t L(s)\, ds. \end{aligned}$$

Because the system is stable and non-preemptive, the relation between the time average number of patients in the population with the average life-years of a patient can be formalized in the following theorem which is the Little's law [Little, 1961].

Theorem 1 *(Little's law) If both λ and ω exist and are finite, then ℓ exists and $\ell = \lambda\omega$.*

In our problem, we are interested in making the infected population size stable at L_0 in the absence of treatment, where L_0 is the expected number of patients in the system. Therefore, the arrival rate should be $\lambda_0 = \frac{L_0}{\omega_0}$, where ω_0 is the average life-years of an untreated patient.

The conventional way of thinking about coverage may be misleading in this scenario. Because one might think that starting from a population of L_0 patients, one needs L_0 treatment doses to reach the coverage level of 100%. We show that the amount of treatment doses needed to treat the entire population is much larger than L_0.

Let $l(d)$ be the expected population size by introducing d treatment doses. We would like to compute the asymptotic behavior of $l(d)$, that is,

$$L = \lim_{d\to\infty} l(d).$$

We know that in this scenario all patients receive treatment. Therefore, by Little's law we have

$$L = \lambda_0 \omega_1,$$

where ω_1 is the expected life-years of a treated patient. By substituting $\lambda_0 = \frac{L_0}{\omega_0}$ we have

$$L = L_0 \frac{\omega_1}{\omega_0}.$$

Since $\frac{\omega_1}{\omega_0} \geq 1$, the expected number of treatment doses needed to treat every patient in the population is greater than or equal to L_0. In Section 3.4, we show that the expected number of treatment doses needed to treat every patient is almost seven times that of the initial number of patients in the population.

Now we derive a formulation for the cumulative incidence-based coverage defined in Section 3.2.2. Let $N^T(t)$ be the total number of patients who received treatment somehow in their lifetime up to time t, $CIBC$ denote the cumulative incidence-based coverage, and PBC denote the prevalence-based coverage. Define

$$CIBC = \lim_{t \to \infty} \frac{N^T(t)}{N^d(t)}.$$

The following proposition relates the conventional prevalence-based coverage with the cumulative incidence-based coverage.

Proposition 1 *Let μ and ω be the average treatment time and lifetime of a patient, respectively. Then we have*

$$CIBC = PBC \times \frac{\omega}{\mu}. \tag{3.1}$$

Proof: Because a $G/G/d$ queueing system with reneging reaches steady state [Koole and Mandelbaum, 2002], we have a constant rate for birth and treatment. Let ρ_b, and ρ_t be the birth rate and treatment rate, respectively. In the steady state, we have

$$CIBC = \lim_{t \to \infty} \frac{\rho_t \times t}{\rho_b \times t} = \frac{\rho_t}{\rho_b}.$$

Also, for the birth rate and treatment rate we have

$$\rho_b = \frac{l(d)}{\omega}, \rho_t = \frac{d}{\mu}.$$

Therefore, the relation between cumulative incidence-based coverage and prevalence-based coverage can be described as

$$CIBC = \frac{\rho_t}{\rho_b} = \frac{\frac{d}{\mu}}{\frac{l(d)}{\omega}} = \frac{d}{l(d)} \times \frac{\omega}{\mu} = PBC \times \frac{\omega}{\mu}.$$

□

Since $\frac{\omega}{\mu} \leq 1$, cumulative incidence-based coverage is always less than or equal to the prevalence-based coverage. Therefore, the conventional way of thinking about coverage always underestimates the amount of resources needed to reach a particular coverage level.

3.4 RESULTS

The steady state HIV-infected population size grows by a factor of 7 (from an initial size of 10,000 to nearly 70,000), relative to a setting where treatment is not available (Figure 2). Above 70,000 doses, all patients who develop HIV disease can be treated, and the fully treated death rate will once again equal the rate of HIV acquisition.

Figure 2 also illustrates the relationship between prevalence-based and cumulative incidence-based coverage and the size of the HIV-infected population: prevalence-based coverage always exceeds cumulative incidence-based coverage, and underestimates the proportion of patients being treated by as much as 29%. The relationship between coverage and the number of doses is nonlinear: with an initial population of 10,000 HIV-infected individuals, 20,000 doses will stabilize at a cumulative incidence-based coverage of approximately 50%, but adding an additional 20,000 doses will only increase cumulative incidence-based coverage to about 80%.

Figure 3 illustrates more directly the relationship between prevalence-based and cumulative incidence-based coverage, the number of doses required to achieve that coverage, and the current context of coverage rates in Sub-Saharan Africa. There is a significant increase in the stable population size from prevalence-based coverage at or below 50% to prevalence-based coverage above 50%. For example, the stable population size when prevalence-based

Table 1: Results for population size, prevalence-based, and cumulative incidence-based coverage

Number of doses	Population size	Prevalence-based coverage	Cumulative incidence-based coverage
0	10000	0	0
5000	14902	0.335526	0.108451
10000	19370.3	0.516254	0.226165
15000	23829.6	0.629469	0.341727
20000	28343.7	0.705625	0.460432
25000	32982.6	0.757974	0.548502
30000	37689.8	0.795971	0.627019
35000	42383.8	0.825788	0.701543
40000	47094.4	0.849358	0.77054
45000	51415.2	0.875228	0.822499
50000	55434.1	0.901973	0.85998
55000	59356.4	0.926607	0.896152
60000	63248.9	0.948633	0.933286
65000	66794.5	0.973134	0.965079
70000	69132.1	1.01255	0.998069

coverage in 50% is approximately 20,000, but the population will rise to nearly 70,000 with sufficient doses to treat all HIV-infected patients who need therapy. Because the population size increases, and because treated patients live longer than those not on therapy, this population increase will require an even more dramatic increase in the number of ART doses. From Figure 3, at 10,000 doses the prevalence-based coverage is just over 50%, but it requires nearly seven times that number to fully cover the population. In Sub-Saharan Africa, nearly 90% of the HIV-infected population live in areas below 60% prevalence-based coverage, implying that the resources required to fully cover the currently infected population in Sub-Saharan Africa is substantially larger than the amount of resources dedicated to this

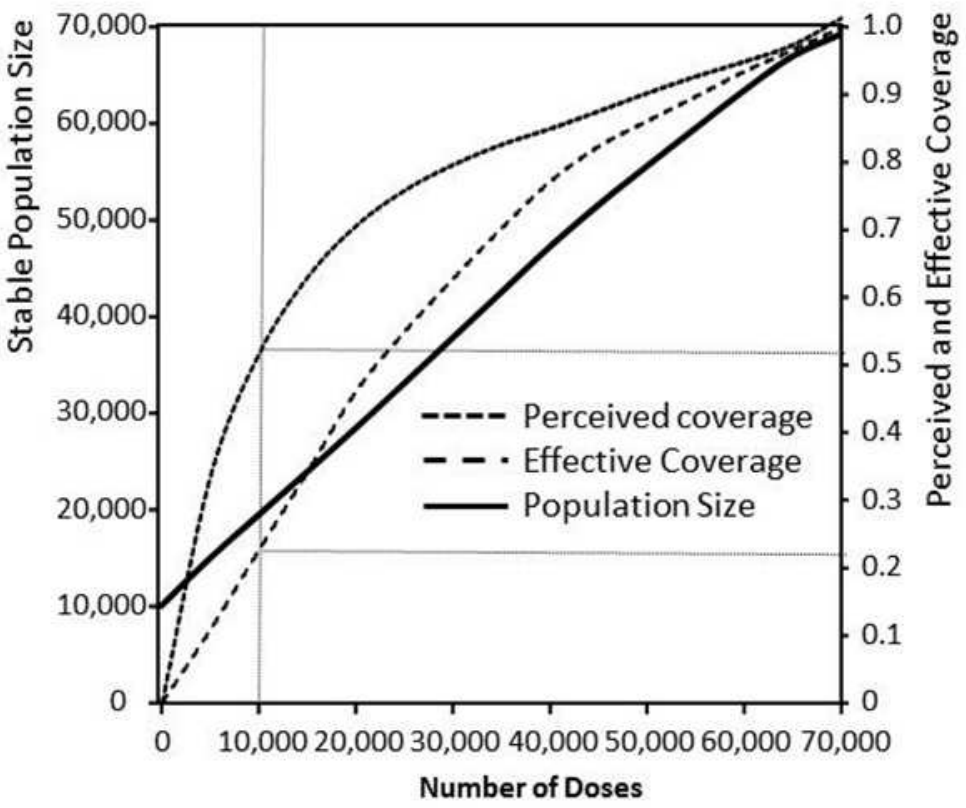


Figure 2: Population size and different coverage definitions

effort and predicted by World Health Organization and other international organizations and charities. This is a direct consequence of increasing the life expectancy due to treatment for HIV patients.

In the end, we compare the results of the simulation model with the queueing model. According to the queueing model, the total population in 100% coverage is equal to the total population with no treatment multiplied by $\frac{\omega_1}{\omega_0}$. The results of running the individual simulation model show that a patient in absence of treatment lives 2.2 years on average, and a patient with treatment lives 15.1 years on average. Therefore, the total population size with 100% coverage should be $\frac{15.1}{2.2} = 6.86$ times of the initial population size. Now we would like to see if there is a significant difference between the result of the simulation model and

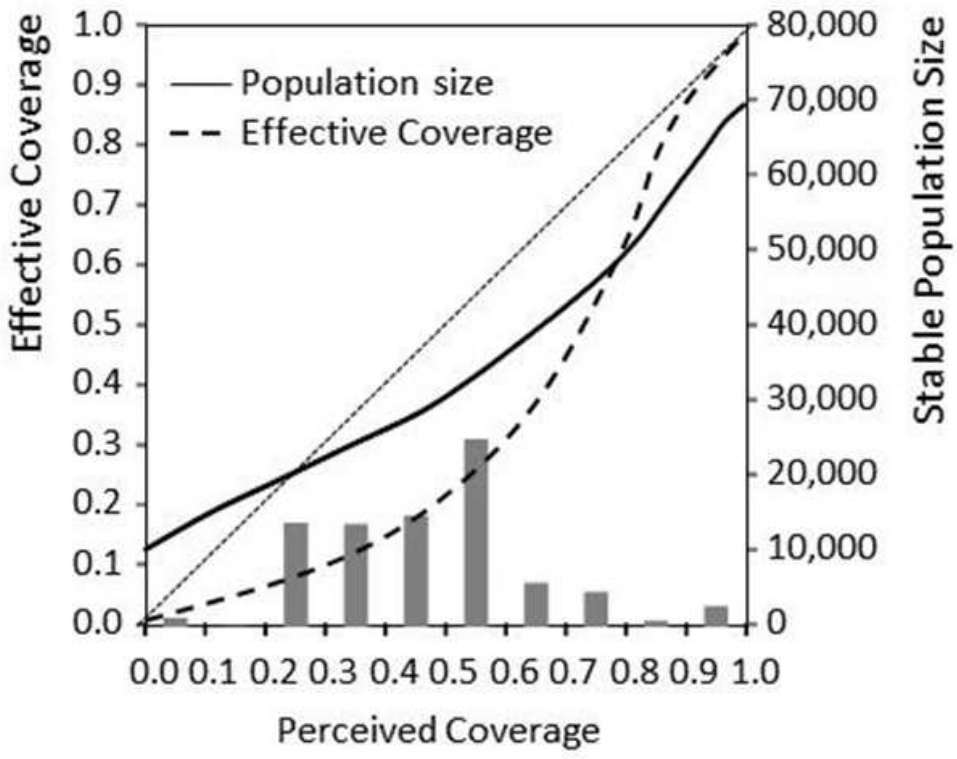


Figure 3: Results of the simulation for prevalence-based and cumulative incidence-based coverage

the queueing model. Since we have 30 samples from the simulation model, we assume that they have a normal distribution and they are independent. At the 0.05 level we fail to reject the null hypothesis, i.e, $H_0 : \mu = 6.86$ (p-value=0.17). Therefore, there is no statistically significant difference between the results of the simulation model and the queueing model.

We also test the results of the simulation for cumulative incidence-based coverage with equation (3.1). Pursuant to this goal, we consider an initial population of 100 patients and introduce treatment doses in different levels. We simulate the system and compute the cumulative incidence-based coverage, the average life-years of a patient in each treatment level, and the average treatment time.

We use equation (3.1) to compute the cumulative incidence-based coverage. Figure 4 compares the result of the simulation model with equation (3.1). As can be seen in Figure 4, the queueing model can predict the cumulative incidence-based coverage generated by the simulation model very well.

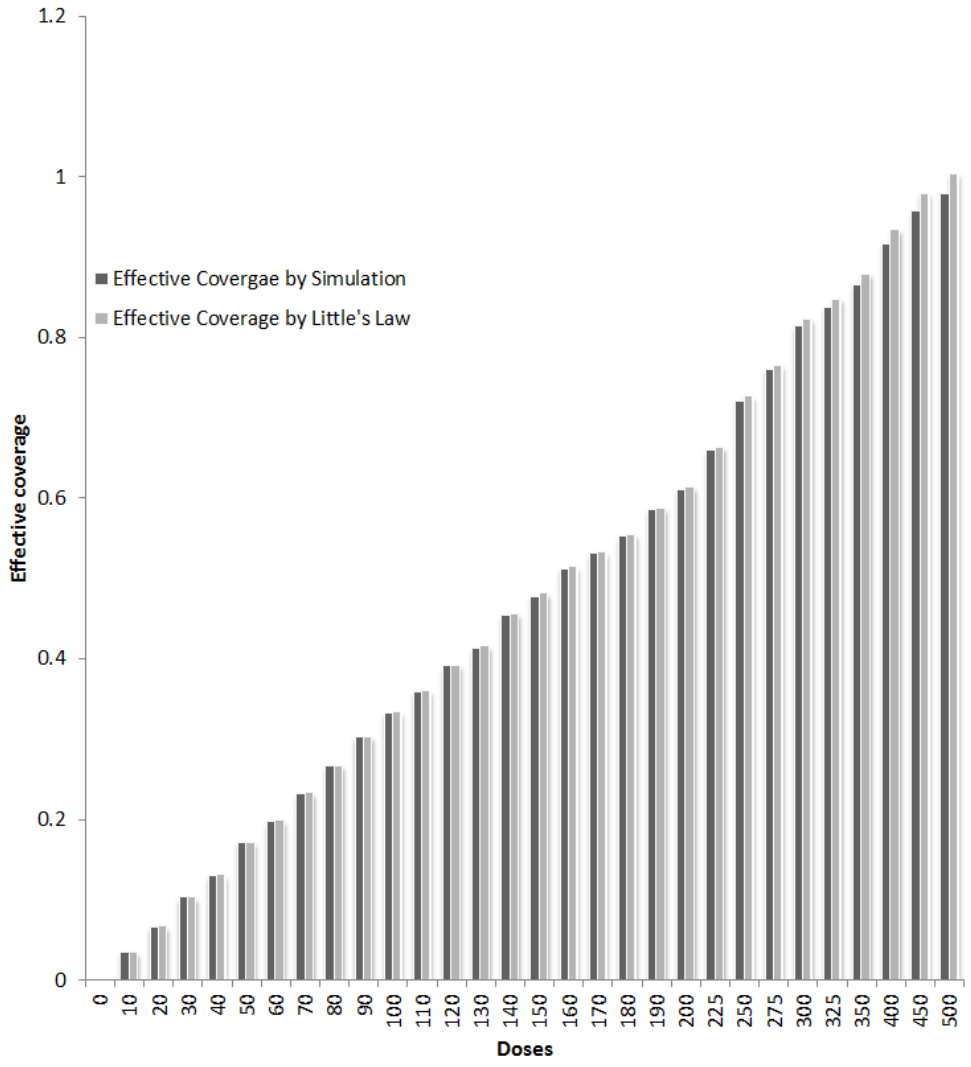


Figure 4: Comparing the results of the queueing model with simulation

3.5 LARGE-SCALE HIV SIMULATION MODEL

The large-scale HIV simulation model extends the simulation model described in Section 3.2 by incorporating transmission dynamics, following the model in Garnett and Anderson [1994] (see Section 4.6 for details of the transmission model). Using the original model's flexibility in accommodating different treatment policies, we can replicate resource-limited conditions and simulate a broad variety of allocation policies.

For parameter calibration we use data from HIV literature in Sub-Saharan Africa. In particular, we use the estimates in Fraser et al. [2007] to compute the probability of transmission per sexual encounter. In addition, following Cohen and Gay [2010], we assume that patients on ART are 70% less likely to transmit the disease. The probabilities in Ciaranello et al. [2008] are used for mother-to-child transmission.

The transition probability from childhood to adulthood is such that the expected childhood period is 15 years (individuals older than 15 years are sexually active [UNAIDS, 2010]). We set the initial number of children to be 40% of the population (as almost 40% of the population are children in Sub-Saharan Africa [CIA, 2010]). Along with Garnett and Anderson [1996], we use four risk groups for adults. In our model, it is assumed that 89% of adults establish one partner while 11% have multiple partners (11% of couples are polygamous in Kenya [Bellan et al., 2013]). For polygamous individuals, we consider 3,5, and 7 partners and the distribution over them is 3:2:1, respectively. Since there is no available data on change of individual's sexual behavior in Sub-Saharan Africa, we assume that adults do not change their risk category. The probability of death for susceptible individuals is such that their expected lifetime equals the life expectancy at birth in Sub-Saharan Africa [World Bank, 2010].

For calibrating the model, we compare the simulation results for prevalence of HIV with the actual prevalence in Kenya from 1990 to 2000. HIV interventions such as condom use, education, and ART were insufficiently available in Kenya during that period, and the actual progression of the disease can be observed in an intervention-free population [UNAIDS, 2010]. After the year 2000, several interventions have been implemented concurrently in Kenya; therefore, data for the marginal effect of one intervention (treatment in our case) on

prevalence is not available. Figure 5 shows the results of the simulation model in the absence of treatment and the actual HIV prevalence in Kenya when no intervention was available. As can be seen, the simulation model results almost match the actual data.

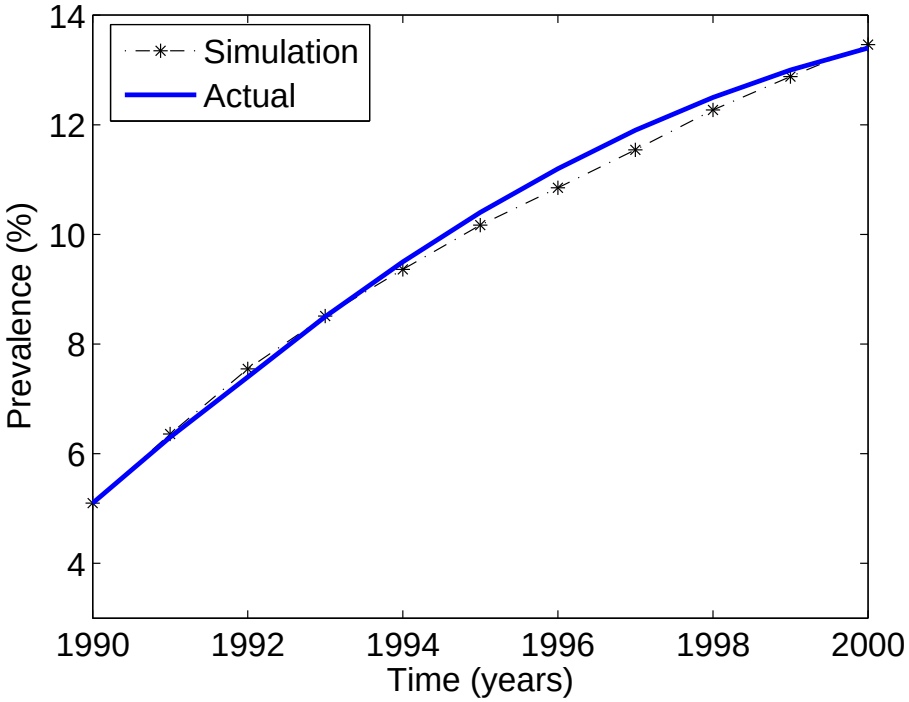


Figure 5: Large-scale HIV simulation calibration

3.6 DISCUSSION

Coverage is not static: it varies through time and depends on the effectiveness of the allocation policy in place, as this impacts the stable population size of HIV-infected individuals. Also, the traditional cross-sectional definition of coverage, which we term "prevalence-based coverage" fails to capture the impact that different levels of resources have on the stable HIV-infected population sizes, and may substantially underestimate the resources required to fully cover a population.

Therefore, an analysis based on the traditional, cross-sectional, static, or prevalence-based concept of coverage might fail to quantify the magnitude of the efforts required to treat the HIV epidemic. Our analysis shows that increasing the coverage level in Sub-Saharan Africa (currently about 50%, on average) is likely to require substantially more resources than implied by current prevalence-based coverage levels. Doubling the current resources available will come nowhere near fully treating the epidemic. We introduce the concept of cumulative incidence-based coverage, the portion of HIV-infected patients who receive treatment at some point in their lifetime, is a more accurate and useful measure of the progress made in HIV care.

This work has several strengths and weaknesses. Our simulation model is calibrated using data from east Africa. The single patient simulation model has demonstrated its ability to predict outcomes in Sub-Saharan Africa. It accurately replicates the progression of the disease in each treatment scenario, and reports prevalence-based and cumulative incidence-based coverage, and the number of doses of ART required to treat a population of a given size. However, the analysis in this work considers only a single ARV regimen, ignoring the effect of the second and third treatment regimens. However, including multiple ART regimens would only compound the problem: second and third line therapies are much more expensive than first line, and patients in the simulation would live even longer in the presence of multiple treatment options. The model does not take into account any impact on the epidemic itself. Although future work will incorporate this aspect, it is difficult to estimate the expected direction of the effect. Increasing treatment decreases the viral load of treated individuals, which decreases the likelihood of transmission. However, treatment also dramatically increases the size of the HIV-infected population, and although treated, nevertheless increases the potential pool of patients who may transmit the infection.

We ignore many capabilities of the underlying HIV model in these simulations. For example, a portion of patients will discontinue their HIV medication because of side effects and toxicity: we assume all treated individuals in the model remain on treatment until death. We re-estimate the results of the model allowing adherence to fall to levels seen in Sub-Saharan Africa and prevalence-based and cumulative incidence-based coverage are slightly less discordant but the overall effect persists.

The increases in treatment of HIV disease is Sub-Saharan Africa has been a massive international effort, requiring the cooperation and dedication of individual health ministries in Africa, multiple charitable foundations, the WHO, many developed nations and the pharmaceutical industry. The results of this research indicate that current published coverage data that indicates that the HIV epidemic in Africa is nearly half-way to being fully treated does not take into account the dynamic effects of coverage on the size of the infected population.

4.0 TIME TO ABANDON NONABANDONMENT? HIV IN SUB-SAHARAN AFRICA

4.1 INTRODUCTION

The current strategy to allocate limited HIV therapies is to assign the available treatment dose to the sickest patients in the population and treat them until they die [WHO, 2012]. Most policy makers follow this nonabandonment strategy because removing a patient from treatment is considered by some to be unethical. Due to resistance, HIV drugs become less effective and the patient becomes sicker; however, under nonabandonment policies, a drug regimen may not be reallocated to another patient who might receive more benefit. Therefore, in resource-limited settings, the nonabandonment policy may be suboptimal. For instance, if a policy maker removes a patient who has developed resistant mutations and is marginally benefiting from treatment, he may be able to assign the treatment dose to another patient who needs it more. In doing so, the health of the patient who starts treatment improves, and he is less likely to transmit the disease. Note that the health of the patient whose treatment is abandoned declines. However, the overall benefit of removing the patient for the society increases.

In this chapter, we quantify the price of nonabandonment policies for HIV treatment in resource-limited settings. We develop a mathematical framework to optimize treatment allocation under resource constraints for a broad class of admissible policies. To quantify the price of nonabandonment, we restrict our attention to two classes of admissible policies: (i) nonabandonment policies, and (ii) abandonment-permitted policies. These allocation problems are intractable because the state spaces of their respective Markov decision process (MDP) formulations are unbounded. We estimate a lower bound on the price as the difference

between the lower bound on the best performance in the abandonment-permitted setting and an upper bound of the best performance in the nonabandonment setting. To solve our problems, we use the linear programming approach to approximate dynamic programming to derive efficient allocation policies. We also provide two techniques to compute the upper bound and guarantee the performance of the proposed policies. We demonstrate that the price of following the nonabandonment strategy in HIV treatment in resource-limited settings is as much as 41% of the total discounted quality-adjusted life expectancy of the population. In addition, we use the large-scale simulation model of Chapter 3 to compare the performance of the proposed policies against relevant benchmarks based on milder assumptions than those required by the MDP model. Finally, we provide insights on the way that our policies assign treatment to patients and reallocate treatment. In particular, we investigate when the ADP policies remove patients from treatment. To the best of our knowledge, this is the first study that incorporates both progression and transmission of HIV for finding near-optimal treatment allocation policies, while considering the population as a whole.

4.2 MODELING THE PRICE OF NONABANDONMENT POLICIES

In this section, we establish a modeling framework for quantifying the performance of different allocation policies through the use of Markov decision processes. Then, we define the price of nonabandonment policies as the gap in performance between the best policies within two classes of admissible policies.

4.2.1 Optimal Allocation of Scarce HIV Treatment

We consider a Markovian discrete-time infinite-horizon model of the progression of an HIV epidemic within a population of heterogeneous individuals. At a broad level, the population is composed of susceptible individuals and infected patients.

Model primitives and assumptions. Susceptible individuals are characterized by a risk index r which categorizes their level of sexual activity, and evolves stochastically in time.

Note that concurrent sexual partnerships is the key driver in the HIV epidemic in Sub-Saharan Africa [Eaton et al., 2011]. Note that children have their own risk index and are assumed to be sexually inactive. We let R denote the set of risk categories which we assume is finite. With respect to treatment, for now we let P denote the finite set of possible *treatment phases* an infected patient may be on at any time. We index treatment phases by p. We assume that patients can start treatment at most once. In Section 4.2.2, we provide precise definitions of this set for different classes of admissible policies.

In addition to their risk, infected patients are also characterized by a health index. For patients who are not on treatment, the health index represents their current CD4 count.[1] Our model discretizes the range of CD4 counts, which is in line with clinical practice [WHO, 2012]. The health index for patients exposed to treatment is represented by a vector with three elements: (i) their CD4 count at the beginning of treatment, (ii) their maximum CD4 count while on treatment, and (iii) their current CD4 count. This choice allows us to model the development of virus mutations resistant to treatment. Note that the development of resistant mutations is not observable in practice, and needs to be inferred from CD4 count evolution. We let H be the finite set of health indices (we assume that susceptible individuals always have the best possible health condition).

Let X_r^t be the total number of susceptible individuals in risk group r at time t, and $Y_{i,p}^t$ that of infected individuals in *infected* state $i \in I$ and treatment phase p, where $I := R \times H$. With this, we let $S^t := (X^t, Y^t)$ denote the state of the population at time period t, where $X^t = (X_r^t : r \in R)$, and $Y^t = (Y_{i,p}^t : i \in I, p \in P)$, and let $\mathcal{S}$ denote the state space (note that $\mathcal{S}$ is unbounded), i.e.,

$$\mathcal{S} := \left\{ S = (X, Y) \in {\mathbb{Z}_+}^{|R|} \times {\mathbb{Z}_+}^{|I||P|} \right\}.$$

We assume that each patient undergoing treatment consumes one dose per period, and let K denote the number of treatment doses available per period, which we assume is constant. In our model, actions move patients from one treatment phase to another, e.g., from pre-treatment to the first phase of being on treatment. We let $A(S)$ denote the set of actions

[1] CD4 count is a measurement of the strength of the immune system and is used as a health indicator in practice.

available to policy makers in state $S \in \mathcal{S}$, and $S(a)$ denote the state of the system after taking an action a. In Section 4.2.2, we explain in detail two sets of admissible actions for the class of policies of interest. In particular, we explain actions sets for the abandonment-permitted and nonabandonment scenarios.

Transition dynamics. We assume that the risk of a susceptible individual changes from r to r' with probability $\eta_{r,r'}$, independent of everything. To model the transition from childhood to adulthood, we let η_r be the probability of a child's transition to risk group r at each period. We let $\rho_{i,i'}^{p,p'}(a)$ denote the probability that a patient in treatment phase p, with risk r and health h evolves to treatment phase p' with risk r' and health h' after action a is taken. We also let $p_r(S,a)$ denote the probability that a susceptible individual in risk category r becomes infected within a decision epoch when the state of the system is S and action a is taken. Following Garnett and Anderson [1994], our model approximates[2] $p_r(S,a)$ by

$$p_r(S,a) \approx \mu_r \sum_{r \in R} \omega_{r,r'} \frac{\sum_{h \in H} \sum_{p \in P} \nu_{r',h,p}\ Y_{r',h,p}(a)}{N_{r'}(S)}, \tag{4.1}$$

where μ_r is the average number of partners a susceptible individual in risk group r establishes, $(\omega_{r,r'} : (r,r') \in R^2)$ represents elements of a *mixing matrix* describing partnership patterns within the population, $\nu_{r',h,p}$ represents the probability of disease transmission in a partnership with an infected patient of risk group r', health state h, and treatment phase p, and $N_{r'}(S)$ denotes the total population of individuals in risk group r'. Further details about the transmission model can be found in Section 4.6, where we provide error bounds for our approximation and show that the maximum error bound is relatively small.

At each period, each adult individual gives birth to a child with probability γ_r. We capture mother-to-child transmission by letting $\kappa_{i,p}$ be the probability that a child born to an infected patient is also infected. Similarly, we assume that each susceptible and infected individual dies within a decision epoch with probabilities d_r, and $d_{i,p}$, respectively. With this notation we have that

$$X_r^{t+1} = X_r^t + B_r - DE_r - TR_r; \quad Y_{i,p}^{t+1} = Y_{i,p}^t + EV_{i,p} - DE_{i,p},$$

[2]We assume that each susceptible individual becomes infected in different partnerships independent of each other.

where B_r denotes total number of children who become adults of risk group r, DE_r denotes total number of susceptible individuals in risk group r who die, TR_r denotes total number of susceptible individuals in risk group r who become infected, $EV_{i,p}$ denotes total number of individuals who evolve to infected state i and treatment phase p, and $DE_{i,p}$ denotes total number of patients who die in a period in infected state i and treatment phase p.

Markov decision process formulation. We consider a policy maker who seeks to maximize the expected discounted cumulative quality-adjusted life years[3] of the population (relative to susceptible individuals). Let $g(S, a)$ denote the immediate reward resulting from applying action $a \in A(S)$ in state $S \in \mathcal{S}$. That is,

$$g(S, a) := \sum_{r \in R} X_r + \sum_{i \in I} \sum_{p \in P} u_{i,p} Y_{i,p}(a), \quad a \in A(S)\,,\ S \in \mathcal{S},$$

where $u_{i,p} \in (0, 1]$ denotes the quality of life experienced by a patient in infected state i and treatment phase p. Let $J_\pi(S)$ denote the expected discounted cumulative QALYs of the population when $S^0 = S$ under policy $\pi \in \Pi$, where Π is the set of stationary allocation policies. That is,

$$J_\pi(S) := \mathbb{E}\left\{ \sum_{t=0}^{\infty} \lambda^t \ g(S^t, \pi(S)) | S^0 = S \right\}, \quad S \in \mathcal{S},$$

where $\pi(S)$ denotes the action selected by an admissible policy π in state S, and $\lambda \in (0, 1)$ is a discount factor. Policy makers seek to maximize $J_\pi(S)$ by solving $V(S) := \sup_\pi \{J_\pi(S)\}$. To ensure the value function V is well defined we assume that rewards are discounted at a rate larger than that of the population growth, as formalized in Assumption 1, which we assume holds throughout the chapter. Note that this assumption is not restrictive. We use real data in our model and the amount of λ should be less than 0.96.

[3]This factor reflects the fact that the quality of life of patients in poor health states or undergoing treatment (and its side effects) is lower than that of healthy untreated patients: see Glasziou et al. [1990].

Assumption 1 *The discount factor λ is such that*

$$\frac{1-\lambda}{\lambda} > \sum_{r\neq 0} \gamma_r - \min\left\{d_{i,p}, d_r \ : \ i \in I \, , \, p \in P\right\}.$$

For any real-valued function $J : \mathcal{S} \to \mathbb{R}$ (note that the domain is the state space), define the following *per-capita* supremum norm

$$\|J\|_{pc} := \sup\left\{\frac{|J(S)|}{|S|+1} \ : \ S \in \mathcal{S}\right\}.$$

The next result extends MDP classical results to characterize the optimal value function and the optimal policy (see Puterman [1994]).

Lemma 1 *There exists $\overline{v} > 0$ and V such that $\|V\|_{pc} < \overline{v}$ and V is the unique solution to*

$$J(S) = \max_{a \in A(S)} \left\{g(S,a) + \lambda \ \mathbb{E}_a\left\{J(S^1)|S^0 = S\right\}\right\}, \quad S \in \mathcal{S}, \tag{4.2}$$

such that $\|J\|_{pc} < \infty$. In addition, there exits an optimal stationary policy π, where

$$\pi(S) \in \arg\max_{a \in A(S)} \left\{g(S,a) + \lambda \ \mathbb{E}_a\left\{V(S^1)|S^0 = S\right\}\right\}, \quad S \in \mathcal{S}.$$

Proof: Define $\delta := \lambda\left(\sum_{r\neq 0}\gamma_r - \min_{(i,p),r}\left\{d_{i,p}, d_r\right\}\right)$. Assumption 1 states that $\delta \in [0,1)$. Note that $g(S,a) \leq |S|+1$ for all $S \in \mathcal{S}$, and that

$$\lambda \ \mathbb{E}_a\left\{(\left|S^1\right|+1)|S^0 = S\right\} \leq \delta(|S|+1), \quad a \in A(S), \, S \in \mathcal{S}.$$

This implies that

$$V(S) \leq (1-\delta)^{-1}(|S|+1), \quad S \in \mathcal{S},$$

and therefore $\|V\|_{pc} \leq \overline{v}$, where $\overline{v} := (1-\delta)^{-1}$ [Puterman, 1994, Proposition 6.10.1, p.234]. Moreover, (4.2) has a unique solution J such that $\|J\|_{pc} < \infty$, and that π is indeed optimal [Puterman, 1994, Theorem 6.10.4, p.236]. We conclude that V satisfies the Bellman equations (4.2). □

4.2.2 Price of Nonabandonment

In this section, we consider two sets of admissible policies to quantify the price of nonabandonment policies in HIV treatment. First is the set of nonabandonment policies, where policy makers treat patients until death. We assume that only one line of treatment is available (this is a mild assumption since second line therapies are much more expensive than the first line therapy [Pujades-Rodriguez et al., 2008]). Thus, patients are either on treatment or not. The second set of admissible policies, known as abandonment-permitted policies, include those where policy makers are able to remove patients from treatment. We restrict our attention to policies that remove patients from treatment at most once. In this setting, patients might be in one of three treatment phases: (i) pre-treatment phase, (ii) on-treatment phase, and (iii) post-treatment phase. Note that patients in the post-treatment phase are not allowed to start treatment. For the purpose of our formulation, we consider $P = \{0, 1, 2\}$, where $p = 0$ denotes the pre-treatment phase, $p = 1$ denotes the on-treatment phase, and $p = 2$ denotes the post-treatment phase.

Define the action space $A(S)$ as

$$A(S) := \left\{ a_{i,p} \ : \sum_{i \in \mathcal{I}} (a_{i,1} - a_{i,2} + Y_{i,1}) \leq K \, , \, 0 \leq a_{i,p} \leq Y_{i,p-1}, \quad i \in \mathcal{I}, \, p \in P \right\}, \quad S \in \mathcal{S},$$

where $a_{i,1}$ represents the number of patients in infected state i moved to treatment, $a_{i,2}$ represents the number of patients in infected state i removed from treatment, and $a_{i,0} = 0$. Note that we do not impose a course of treatment in our model, but rather let the model decide when the patient should be removed from treatment, if ever (see Section 4.5.2).

The set of admissible policies for the nonabandonment case is represented by $\Pi = \{\pi : \pi(S) \in A(S); a_{i,2} = 0\}$, where $Y_{i,p}(a) = Y_{i,p} + a_{i,p}$. For the abandonment-permitted case the set of admissible policies is represented by $\overline{\Pi} = \{\pi : \pi(S) \in A(S)\}$, where $Y_{i,p}(a) = Y_{i,p} + a_{i,p} - a_{i,p+1}$. The price of nonabandonment (PoN) can be expressed as

$$PoN = \max_{\pi \in \overline{\Pi}} J_\pi(S) - \max_{\pi \in \Pi} J_\pi(S). \tag{4.3}$$

PoN measures the benefit that the society might obtain in terms of total discounted quality of life by allowing policy makers to remove patients from treatment. We interpret it as

the price that society pays by following the nonabandonment policy, where policy makers keep patients who have started treatment on therapy until they die. In the next section, we provide an algorithmic approach for finding lower bounds and upper bounds.

4.3 APPROXIMATE SOLUTIONS AND PERFORMANCE GUARANTEE

Computing PoN is intractable as it involves solving MDP formulations with countable state spaces. Instead, we compute a lower bound on PoN by the difference between a lower bound on the best performance in the abandonment-permitted setting and an upper bound for that in the nonabandonment setting. That is,

$$PoN \geq \underline{\phi}\left(\max_{\pi\in\overline{\Pi}} J_\pi(S)\right) - \overline{\phi}\left(\max_{\pi\in\Pi} J_\pi(S)\right), \tag{4.4}$$

where $\underline{\phi}(.)$, and $\overline{\phi}(.)$ represent the lower bound and upper bound, respectively. To compute a lower bound, we use the linear programming approach to ADP to derive efficient allocation policies. To compute an upper bound we consider a relaxation of our formulation, as well as a natural upper bound from ADP.

4.3.1 Lower Bound

We adapt the linear programming approach to approximate dynamic programming to compute an efficient allocation policy, and use its performance as a lower bound. Note that the same approach can be used to find a lower bound for the nonabandonment setting. Similar to the case of finite state space and bounded rewards [Puterman, 1994, p.148], one can show that $J \geq V$ for any J such that $\|J\|_{pc} < \infty$, and

$$J(S) \geq \max_{a\in A(S)} \left\{g(S,a) + \lambda\, \mathbb{E}_a\left\{J(S^1)|S^0 = S\right\}\right\}, \quad S \in \mathcal{S}.$$

Consider a distribution $\{c(S) : S \in \mathcal{S}\}$ such that $c(S) > 0$ for all $S \in \mathcal{S}$. Proposition 2 provides an alternative characterization of the value function.

Proposition 2 *Given $U \geq \overline{v}$, then V is the unique solution to*

$$\min \quad \sum_{S \in \mathcal{S}} \frac{c(S)}{|S|+1} \, J(S) \tag{4.5a}$$

$$s.t.$$

$$J(S) \geq g(S,a) + \lambda \, \mathbb{E}_a \left\{ J(S^1) | S^0 = S \right\}, \quad a \in A(S), \, S \in \mathcal{S}, \tag{4.5b}$$

$$|J(S)| \leq (|S|+1)U, \quad S \in \mathcal{S}. \tag{4.5c}$$

Proof: Define the dynamic programming operator T by

$$(TJ)(S) := \max_{a \in A(S)} \left\{ g(S,a) + \lambda \mathbb{E}_a \left\{ J(S^1) | S^0 = S \right\} \right\}, \quad S \in \mathcal{S}.$$

Suppose $J' \geq J$ component-wise, then $(TJ') \geq (TJ)$. In addition, Assumption 1 implies that (see proof of Lemma 1) T is a contraction in the Banach space induced by $\| \cdot \|_{pc}$ [Puterman, 1994, Theorem 6.10.4, p.236]. Moreover, for any J such that $\|J\|_{pc} < \infty$ one has that

$$\lim_{n \to \infty} \|T^n J - V\|_{pc} = 0.$$

Note that V is a feasible solution to (4.5), and that all feasible solutions attain finite objectives. Consider a feasible J; since $J \geq TJ$ one has that $TJ \geq T^2 J \geq T^3 J \geq \ldots$. However, the sequence $T^k J$ converges to V, thus we conclude that $J \geq V$, which implies that

$$\sum_{S \in \mathcal{S}} \frac{c(S)}{|S|+1} J(S) \geq \sum_{S \in \mathcal{S}} \frac{c(S)}{|S|+1} V(S),$$

implying that V is the unique optimal solution to (4.5). □

Formulation (4.5) has countably many constraints and variables. We approximate its solution in two steps. First, we approximate the value function V using an affine combination of basis functions, so as to reduce the number of variables. Second, we limit the number of constraints by sampling the states that are most likely to be visited by the optimal policy. In addition, we use structural properties of the optimal policy under such approximation to limit the number of actions worthy of consideration (note that $A(S)$ grows exponentially with the size of S).

Value function approximation. We approximate V using an affine combination of basis functions:

$$\hat{V}_\alpha(S) := \alpha_0 + \sum_{i\in I}\sum_{p\in P} \alpha_{i,p}\, Y_{i,p} + \sum_{r\in R} \alpha_r\, X_r, \quad S \in \mathcal{S}. \tag{4.6}$$

In this approximation, one may interpret $\alpha_{i,p}$ as the marginal change in the expected QALYs of the population if one patient is added to infected state i and treatment phase p. Similar interpretation holds for α_r. Our first approximation consists of restricting attention to feasible solutions to (4.5) of the form $\hat{V}_\alpha$. One can show that imposing $|\hat{V}_\alpha(S)| \leq (|S|+1)U$, for all $S \in \mathcal{S}$ is equivalent to $\|\alpha\|_\infty \leq U$, where $\|.\|_\infty$ denotes the uniform norm.

By considering the affine value function approximation, the optimal allocation policy is of state-dependent priority-rule type.

Proposition 3 *For any α and state S, the action maximizing the right-hand side of (4.5b), when the value function is replaced by the approximation in (4.6), is that assigning treatment according to the priority rule induced by the rating*

$$\sigma_{i,p}(\alpha, S) := (-1)^p \Bigg(\alpha_{i,p} d_{i,p} - \alpha_{i,p-1} d_{i,p-1} + \sum_{i'\in I} \alpha_{i',p}\rho^p_{i,i'} - \alpha_{i',p-1}\rho^{p-1}_{i,i'} + \frac{\sum_{r'} \alpha_{r'} X_{r'} \mu_{r'} \omega_{r',r}}{N_r} (\nu_{r,h,p} - \nu_{r,h,p-1}) - (u_{i,p} - u_{i,p-1}) \Bigg),$$

for all $i \in I$, $p \in P$.

Proof: Consider the set of constraints (4.5b) associated with $S \in \mathcal{S}$. We have

$$\mathbb{E}_a\left\{X^1_r | S^0 = S\right\} = D_r(S) - X_r \mu_r \sum_{r'}\sum_{h}\sum_{p} \frac{\omega_{r,r'}\nu_{r',h,p}}{N_{r'}} (a_{r',h,p} - a_{r',h,p+1}),$$

$$\mathbb{E}_a\left\{Y^1_{i,p} | S^0 = S\right\} = D_{i,p}(S) - d_{i,p}(a_{i,p} - a_{i,p+1}) + \sum_{i'\in I} \rho^p_{i',i}(a_{i',p} - a_{i',p+1}), \quad i \in I,\, p \in P.$$

Using $\mathbb{E}_a\left\{Y^1_{i,p} | S^0 = S\right\}$ and $\mathbb{E}_a\left\{X^1_r | S^0 = S\right\}$, one can rewrite (4.5b) as a single nonlinear constraint

$$\sum_{i\in I}\sum_{p\in P} \left((\alpha_{i,p} - u_{i,p})\, Y_{i,p} - \lambda \alpha_{i,p} D_{i,p}(S)\right) + \sum_{r\in R} \left((\alpha_r - 1)\, X_r - \lambda \alpha_r D_r(S)\right) + (1-\lambda)\alpha_0 \geq$$

$$\lambda \max_{a\in A(S)} \left\{ \sum_{i\in I}\sum_{p\in P} \alpha_{i,p} \left(u_{i,p}(a_{i,p} - a_{i,p+1}) + \sum_{i'\in I} \rho^p_{i',i}\,(a_{i',p} - a_{i',p+1}) - d_{i,p}\,(a_{i,p} - a_{i,p+1}) \right) \right\}.$$

For a fixed α, the right-hand side above can be rewritten as the maximization of a linear function of α

$$\max\left\{\sum_{i\in I}\sum_{p\in P}\sigma_{i,p}(\alpha,S)\ z_{i,p}\ :\ \sum_{i\in I}(z_{i,1}+z_{i,2})\le K\ ,\ 0\le z_{i,p}\le Y_{i,p-1}\quad i\in I\ ,\ p=1,2\right\}. \tag{4.7}$$

The maximization problem in (4.7) is a bounded knapsack problem with equal weights; therefore, it is greedily solvable. Thus, for each state S, $\sigma_{i,p}(\alpha,S)$ induces a strict priority-rule policy. This proof is for the general case. One can use a similar argument for the nonabandonment case. □

Each σ is an ordered list of (i,p) pairs, so for each S, the allocation is found by considering (i,p) pairs in the order given by σ. Note that in our settings, transitions in treatment phases are triggered exclusively by actions, thus, it suffices to consider $\rho^{p}_{i,i'}=\rho^{p,p'}_{i,i'}$. Proposition 3 shows that rather than considering all actions in $A(S)$, we only need to consider those induced by priority lists.

Example 2 *Suppose that* $R=\{1,2\}$, $H=\{1\}$, $K=10$, *and consider abandonment-permitted policies. Table 2 shows a possible state and priority list (e.g., patients in state* $(r=1,h=1,p=1)$ *have the highest priority). Following such a priority list, we see that all patients in state* $(r=1,h=1,p=1)$ *receive treatment, as well as three patients in state* $(r=2,h=1,p=0)$. *Note that four patients in state* $(r=2,h=1,p=1)$ *do not receive treatment despite being currently on treatment, that is, they are moved to post-treatment phase.*

Table 2: Assigning treatment according to a priority list

Priority	r	h	p	Number of patients	Allocated treatment
1	1	1	1	4	4
2	2	1	0	3	3
3	2	1	1	7	3
4	1	1	0	2	0

Define Σ as the set of all possible permutations of elements in $I \times P$. For $\sigma \in \Sigma$ and $S \in \mathcal{S}$, define

$$Y^{\sigma}_{i,p}(S) := D_{i,p}(S) - d_{i,p}\left(a^{\sigma}_{i,p}(S) - a^{\sigma}_{i,p+1}(S)\right) + \sum_{i'} \rho^{p}_{i',i}\left(a^{\sigma}_{i',p}(S) - a^{\sigma}_{i',p+1}(S)\right),$$
$$X^{\sigma}_{r}(S) := D_{r}(S) - X_r \mu_r \sum_{r'}\sum_{h}\sum_{p} \frac{\omega_{r,r'}\nu_{r',h,p}}{N_{r'}}(a^{\sigma}_{r',h,p}(S) - a^{\sigma}_{r',h,p+1}(S)),$$

where $a^{\sigma}(S) \in A(S)$ denotes the greedy ART allocation associated with permutation σ (as illustrated in Example 2), and $D_{i,p}(S)$ and $D_r(S)$ are finite state-dependent constants.

Constraint sampling. By considering the priority-rule policies and imposing constraints (4.5b) for a finite sample of states, one can write the approximation problem as

$$RLP(c,\overline{\mathcal{S}}): \quad \min \quad \sum_{S\in\mathcal{S}} \frac{c(S)}{|S|+1}\left(\alpha_0 + \sum_{i\in I}\sum_{p\in P}\alpha_{i,p}\, Y_{i,p} + \sum_{r\in R}\alpha_r\, X_r\right) \tag{4.8a}$$

$$s.t.$$

$$D(S) + (1-\lambda)\alpha_0 + \sum_{i\in I}\sum_{p\in P}\alpha_{i,p}\left(Y_{i,p} - \lambda Y^{\sigma}_{i,p}(S)\right) + \sum_{r\in R}\alpha_r\left(X_r - \lambda X^{\sigma}_{r}(S)\right) \geq 0, \quad \sigma\in\Sigma,\ S\in\bar{\mathcal{S}}, \tag{4.8b}$$

$$\|\alpha\|_{\infty} \leq U, \tag{4.8c}$$

where $D(S)$ depends only on S, and $\bar{\mathcal{S}}$ corresponds to m states in $\mathcal{S}$ sampled according to the distribution c [de Farias and Van Roy, 2004]. We design an exact algorithm to find the optimal solution of $RLP(c,\overline{\mathcal{S}})$, which we use to construct an efficient allocation policy.

Algorithmic approach. $RLP(c,\overline{\mathcal{S}})$ is a linear program with $n := |I|\,|P| + 2\,|R| + 1$ variables, and $|\Sigma|\,m + 2n$ constraints. Recall that Σ contains all permutations of $I \times P$, in particular, $|\Sigma| = (|I|\,|P|)!$. In our numerical study in Section 4.4, we have $|\Sigma| = 300! \approx 10^{614}$ ($|\Sigma| = 25! \approx 10^{25}$ policies in nonabandonment setting) so one cannot explicitly formulate $RLP(c,\overline{\mathcal{S}})$.

Let $\overline{\Sigma}(S)$, a subset of Σ, be a set of priority-rule policies for state S. Solve $RLP(c,\overline{\mathcal{S}})$ for a fixed c and $\overline{\mathcal{S}}$, imposing constraints (4.8b) only for $\sigma \in \overline{\Sigma}(S)$, and let α denote the optimal solution to (4.8). If for each state S the priority $\sigma(\alpha, S)$ is included in $\overline{\Sigma}(S)$, then one concludes that α is optimal when one includes all constraints in $RLP(c,\overline{\mathcal{S}})$ (i.e., those associated with policies in $\Sigma \setminus \overline{\Sigma}(S)$); on the other hand, if $\sigma(\alpha, S)$ is not included in $\overline{\Sigma}(S)$,

then one should add $\sigma(\alpha, S)$ to the set of "plausible" policies. The observation above allows us to solve $RLP(c, \overline{\mathcal{S}})$ iteratively: We use a few clinically based guidelines (such as WHO recommendations) to construct an initial set of permutations $\overline{\Sigma}(S)$ for each $S \in \overline{\mathcal{S}}$. If $\sigma(\alpha, S) \notin \overline{\Sigma}(S)$, where α solves $RLP(c, \overline{\mathcal{S}})$, then we add $\sigma(\alpha, S)$ to $\overline{\Sigma}(S)$ and re-solve. Since $|\Sigma| < \infty$, the outcome of the procedure is the solution to $RLP(c, \overline{\mathcal{S}})$, although the number of steps necessary to converge will depend on the initial set of policies considered (in our numerical experiments in Section 4.4.1, we find that only a reasonably small number of priority lists is added prior to convergence). Algorithm 1 formalizes this iterative procedure.

In addition to the above algorithm, we add a set of *empirical lower bound constraints* $\hat{V}_\alpha(S) \geq \bar{V}_\alpha(S)$ for a relatively small subset $\hat{\mathcal{S}} \subset \overline{\mathcal{S}}$ to the $RLP(c, \overline{\mathcal{S}})$, where $\bar{V}_\alpha(S)$ is the value function calculated by the ADP simulation under a policy induced by α. The objective here is to recover the bounding property of the approximation, which might be lost due to insufficient sampling of constraints. Our results in Section 4.4.1 indicate that these constraints, which we believe are novel in the ADP literature, significantly improve the quality of the approximation.

Algorithm 1 Solving $RLP(c, \overline{\mathcal{S}})$

For each $S \in \overline{\mathcal{S}}$ find an initial set of policies $\overline{\Sigma}(S)$.

Let α be a solution to $RLP(c, \overline{\mathcal{S}})$.

while $\sigma(\alpha, S) \notin \overline{\Sigma}(S)$ for all S **do**

Set $\overline{\Sigma}(S) := \overline{\Sigma}(S) \cup \{\sigma(\alpha, S)\}$.

Re-solve $RLP(c, \overline{\mathcal{S}})$.

Return α as an optimal solution to $RLP(c, \overline{\mathcal{S}})$.

We now discuss how to select c and $\overline{\mathcal{S}}$. de Farias and Van Roy [2004] show that c regulates the quality of the approximation and can be used to target some regions in $\mathcal{S}$ where we need good approximations. We are interested in regions in the state space that are more likely to be visited by the optimal policy, which is not available. We select c and $\overline{\mathcal{S}}$ so that: (i) its computation is tractable; and (ii) it generates a policy via solving $RLP(c, \overline{\mathcal{S}})$ that is likely to visit states that have larger weights according to c. Regarding (i), we use $\hat{c}_{\pi,T}$ as the empirical counterpart of c, where π is an allocation policy and T is the simulation period

(see Section 4.7 for details). Regarding (ii), we use the following procedure: Starting from a policy π^0, we use $\hat{c}_{\pi^0,T}$ to sample m states, which we denote by $\mathcal{S}^0$, to formulate and solve $RLP(\hat{c}_{\pi^0,T}, \mathcal{S}^0)$ via Algorithm 1. At each iteration k, an optimal solution α^k is used to compute $\hat{c}_{\pi^k,T}$. We sample new states according to $\hat{c}_{\pi^k,T}$ and repeat the procedure until $|\alpha^k - \alpha^{k-1}| \leq \epsilon$. We address the convergence of Algorithm 2 in Section 4.4.1.

Algorithm 2 Finding efficient allocation policies

Initialize π^0 and set $k = 0$.

while $|\alpha^k - \alpha^{k-1}| > \epsilon$ **do**

Compute $\hat{c}_{\pi^k,T}$ and sample $\mathcal{S}^k$ according to $\hat{c}_{\pi^k,T}$.

Add $\hat{V}(S) \geq \bar{V}_{\alpha^k}(S),\ S \in \hat{\mathcal{S}}$ to $RLP(\hat{c}_{\pi^k,T}, \mathcal{S}^k)$.

Solve $RLP(\hat{c}_{\pi^k,T}, \mathcal{S}^k)$ and set $\alpha^{k+1} := \alpha^*$.

Set $k := k + 1$.

Return α^k.

4.3.2 Upper Bound

As noted in Section 2.2, finding upper bounds is hard, and existing techniques do not apply in our setting. In this section, we propose two techniques to compute upper bounds for our problem.

Relaxation-based upper bound. Consider our formulation with every infected patient replaced by two "clones". The first clone (type 1) contributes to the transmission of the disease and does not contribute to value function. We assume that the health progression for type 1 clones is stochastically equivalent to that of a patient not on treatment. The second clone (type 2) adds to the value function and does not contribute to transmitting the disease. We assume that type 2 clones are always in the best health state. Upon infection, susceptible individuals are replaced by two clones as well. Figure 6 illustrates this procedure.

We assign treatment to each type of clones separately. Note that type 1 clones who are on treatment are less likely to infect susceptible individuals though their health progression

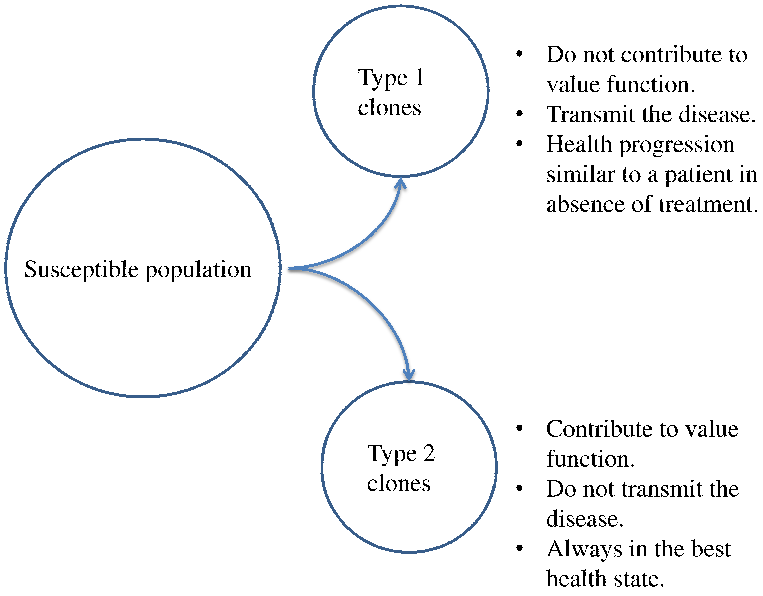


Figure 6: Schematic view of the procedure for finding the upper bound

is not affected by treatment. We show that the optimal policy to assign treatment doses to type 1 clones to maximize the value function is of priority-rule type. This will enable us to assign treatment doses to clone 1 patients according to priority-rule type list. The assignment procedure is similar to Example 2.

Lemma 2 *If $d_r \leq d_{i,p}$ for all r, i, p and we have random mixing, the optimal policy to treat type 1 clones is giving treatment according to priority rule induced by the rating*

$$\overline{\sigma}_{r,h} := c_r(\nu_{r,h,0} - \nu_{r,h,1}) \quad \forall r, h.$$

Proof: In random mixing, the optimal one-step policy can be obtained by solving the following problem

$$\max \left\{ \sum_r \sum_h c_r(\nu_{r,h,0} - \nu_{r,h,1}) a_{r,h} : \sum_r \sum_h a_{r,h} \leq K, \;\; a_{r,h} \geq 0 \right\},$$

which is a knapsack problem with uniform weights that can be solved greedily. One can also show by sample path arguments that a susceptible individual is more favorable for the value function than an infected individual since $d_r \leq d_{i,p}$, and infected individuals transmit the disease. Therefore, the optimal one-step policy is optimal. □

Since type 2 clones are always in the best health state, treatment is almost irrelevant. However, patients on treatment are less likely to die. Therefore, it is optimal to assign all treatment doses, no matter to whom. We assume that $\nu_{r,h,p} = \nu_{r,h',p}$ for all h and h'. In this setting, we have an upper bound for the value function.

Proposition 4 *If all assumptions of the new formulation hold and we have random mixing, the solution to the system described above provides an upper bound for the stochastic dynamic programming problem.*

Proof: We show that at each time in the system described in Proposition 4: (i) susceptible individuals are less likely to become infected, and (ii) infected patients are less likely to die. Therefore, by following a sample path argument, this system has more expected individuals at each time than the original system. On one hand, treated patients live longer and they have more opportunities to infect susceptible individuals. Therefore, to eliminate this effect of treatment on transmission, we consider the health progression of type 1 clones to be similar to that of a patient in absence of treatment. On the other hand, treatment reduces infectivity and patients on treatment are less likely to transmit the disease. We capture this effect by finding the optimal policy to treat type 1 clones by Lemma 2. Thus, at each time susceptible individuals are less likely to become infected. Note that type 1 clones do not contribute in value function. In addition, type 2 clones are always in the best health state and they are more likely to live longer than patients in the original system. Therefore, at each time we have more infected patients who contribute in calculating the value function. □

Proposition 4 provides an upper bound when mixing is random. We use this upper bound as an approximated upper bound for the settings where mixing is not random.

Heuristic upper bound. We know that when all states appear in (4.8), the approximate value function provides an upper bound for the actual value function, i.e., $\hat{V}_\alpha(S) \geq V(S)$.

Since we sample finitely many states, this property does not necessarily hold. Our second bound is based on the conjecture that as more states are included in the sample, the approximation approaches an upper bound, and that the marginal change in the approximation is decreasing in the size of the sample. Let $\hat{V}_{\alpha(m)}(S)$ be the approximate value function, where $\alpha(m)$ is the solution of Algorithm 2 by considering m sample states. We use the observation above to design an iterative procedure: We start from a finite sample state. At each iteration we double the sample size and calculate $\hat{V}_{\alpha(2m)}(S)$. If $\left|\hat{V}_{\alpha(2m)}(S) - \hat{V}_{\alpha(m)}(S)\right| \leq \epsilon$, then we stop and consider $\hat{V}_{\alpha(m)}(S)$ as the heuristic upper bound. Algorithm 3 formalizes this approach.

Algorithm 3 Heuristic upper bound

Set $m = 1000$, and find $\hat{V}_{\alpha(m)}(S)$ via Algorithm 2.

while $\left|\hat{V}_{\alpha(2m)}(S) - \hat{V}_{\alpha(m)}(S)\right| > \epsilon$ **do**

Establish new $\mathcal{S}$ by doubling the sample size.

Solve (4.8) via Algorithm 2 to find $\hat{V}_{\alpha(2m)}(S)$.

Return $\hat{V}_{\alpha(m)}(S)$.

4.4 NUMERICAL STUDY

In this section, we estimate PoN by using a lower bound on the performance in the abandonment-permitted setting and an upper bound for that in the nonabandonment setting. In the process, we show that the the policies produced by the ADP framework are close to optimal.

4.4.1 Computational Issues

Each decision epoch is considered to be three months Shechter et al. [2008]. Recall that the health of patients is represented by the CD4 count. We discretize the CD4 count range into five categories used in practice by policy makers. Therefore, we have five health categories

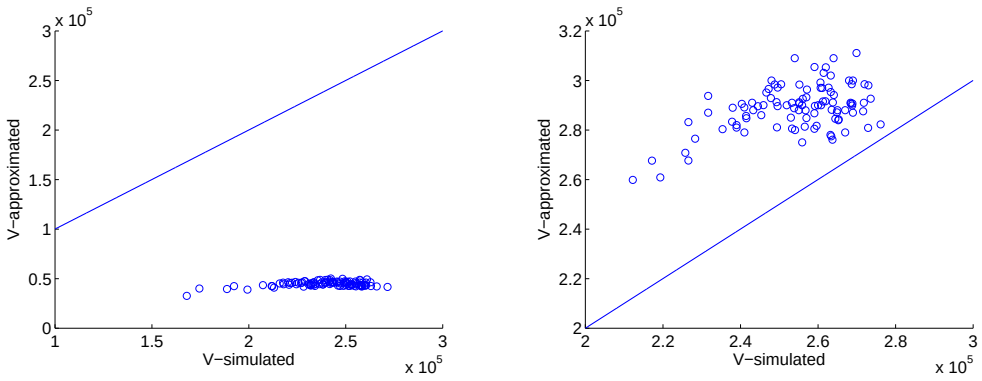
for the pre-treatment and post-treatment phases, and 55 triplet[4] health categories for on-treatment phase: with this, one has that $|\Sigma| := 300! \approx 10^{614}$ ($|\Sigma| := 25! \approx 10^{25}$ in the nonabandonment setting). We use the Braithwaite et al. [2011] simulation model, which is validated with data from western Kenya, to simulate the progression of the disease for 100,000 patients in order to estimate the progression probabilities. The calibration of other parameters in the model is similar to that in the large-scale HIV simulation model (see Section 3.5). We initialize $\overline{\Sigma}(S)$ by using WHO recommendations, and we set $T = 75$ years, $\lambda = 0.96$, and $\left|\overline{\mathcal{S}}\right| = 1000$.

Within Algorithm 2, we consider a smooth policy update, so that $\alpha^k = \alpha^{k-1} + (\alpha^k - \alpha^{k-1})k^{-3/4}$. This type of policy update has been used in similar works to guarantee convergence[5]: see, for instance, Farias et al. [2011]. Considering the interpretation of α as the total discounted life-years contributed by an individual ($\sum_{j=0}^{\infty} \lambda^t = 25$), we choose $U = 250$. We select S^0 so that it represents the current state of the HIV epidemic in Sub-Saharan Africa. In our numerical experiments, we focus on maximizing life expectancy, i.e., we set $u_{i,p} = 1$ for all $(i, p) \in I \times P$.

In our experiments, we observe that our algorithms converge rapidly across all coverage levels: For example, in Algorithm 2, for each state $S \in \mathcal{S}$ the algorithm adds less than 10 policies to $\overline{\Sigma}(S)$ prior to convergence (this is despite the fact that $|\Sigma|$ is huge). We illustrate the effect of empirical lower bound constraints on the quality of the value function approximation in Figure 7. On the x-axis we show $\bar{V}_{\alpha^\star}(S)$ which is the simulated value function under $\alpha^\star$, where $\alpha^\star$ is the optimal solution to the approximation problem. On the y-axis we show $\hat{V}_{\alpha^\star}(S)$ which is calculated by plugging α^* into (4.6) for 100 states chosen randomly from $\overline{\mathcal{S}}$. As can be seen, adding the empirical lower bound constraints significantly improves the quality of our approximations.

[4]Recall that for the health of on-treatment patients we consider a vector of three components, where each component is a CD4 category and has 5 possibilities. One component is maximum CD4 count and should be greater than or equal to other two components. Therefore, we have 55 possibilities.

[5]In our implementation, this smooth update is implemented after a few iterations and has little impact on the quality of the approximation.



(a) Without empirical lower bound constraints

(b) With empirical lower bound constraints

Figure 7: Comparing approximated and simulated value function

4.4.2 Benchmark Policies

We use WHO recommendations as a benchmark, and consider its performance as our baseline. Following WHO guidelines, drugs are assigned upon availability to the sickest patients in the population, and the patient receives treatment until she dies. In addition, treatment initiation is recommended only when a patient's CD4 count goes below 350 cells/mm^3 [WHO, 2012].

State-independent priority-rule policies are appealing in practice, and most policy makers are interested in this type of policy [Bertsimas et al., 2013]. For the second benchmark, we restrict our attention to state-independent priority-rule policies and provide two methods for finding state-independent allocation policies.

In the first method, we design a state-independent priority list by exploiting the single-patient model. For each infected state i we run the Braithwaite et al. [2011] simulation model to find the expected lifetime of a patient with and without treatment. We consider a priority list that prioritizes patients according to the benefit obtained by starting treatment.

In the second method, we consider an initial priority list, and simulate the system according to the priority list and find the objective function. Then, we randomly select two elements in the list and exchange them. We simulate the system according to the new list,

and if the performance of the new list is better than the previous list, we accept the new list. We continue this procedure to find an efficient allocation policy. In our numerical experiments in Section 4.4.3, we run the procedure for 1000 iterations. In addition, for designing state-independent benchmark policies, we find an initial priority list by running the single-patient model and use it as an initial priority list for the second method. Note that we design state-independent benchmarks in both nonabandonment and abandonment-permitted settings.

4.4.3 Results

Our results show that ADP policies outperform WHO recommendations by as much as 5% when policy makers follow the nonabandonment strategy. For guaranteeing the quality of the ADP policies, we calculate the heuristic upper bound in this setting. Table 3 shows the improvement in the objective function and the heuristic upper bound in each coverage level.

Table 3: Nonabandonment ADP policies performance compared to WHO recommendations (%)

Coverage	15	28	47	58	67	84	95
State-independent benchmark	0.9	1.2	3.0	3.6	4.6	4.6	4.8
ADP	1.2	2.4	4.0	4.1	4.9	4.9	4.8
Heuristic upper bound	17.2	14.8	12.6	9.2	6.5	5.6	5.3

We also test the performance of ADP policies in the abandonment-permitted setting where policy makers may remove patients from treatment. Table 4 shows the improvement in the objective function, relaxation-based upper bound, and heuristic upper bound in each coverage level. In this setting, the ADP policies outperform WHO recommendations by as much as 62%. Table 5 shows PoN lower bound estimates for each coverage. As can be seen, the price of nonabandonment policies is as much as 41% of total discounted QALYs of the

Table 4: Abandonment-permitted ADP policies performance compared to WHO recommendations (%)

Coverage	15	28	47	58	67	84	95
State-independent benchmark	2.1	3.2	4.2	3.7	2.9	0.3	-2.6
ADP	16.0	55.2	52.6	50.5	45.0	42.8	37.5
Relaxation-based upper bound	60.9	62.2	59.3	57.0	52.6	48.1	43.2
Heuristic upper bound	67.7	64.4	61.6	56.3	51.9	48.1	43.3

whole population. Note that in the 15% coverage level, the lower bound on the price of nonabandonment is negative. This is due to the loose upper bound in the nonabandonment setting in that coverage level.

Table 5: Price of nonabandonment policies (%)

Coverage	15	28	47	58	67	84	95
Price	-1.2	40.4	40.0	41.3	38.5	37.2	32.2

After developing resistant mutations, HIV-infected patients marginally benefit from treatment. Keeping patients on treatment until they die hinders the opportunity of assigning the treatment dose to other patients who might benefit more. Our results show that the opportunity cost in this setting is huge. Removing a patient from treatment may be unethical to the patient. However, keeping a patient on treatment until she dies may be unethical to other patients who need treatment. By removing patients from treatment, we can treat a greater proportion of the infected population, and this results in more QALYs for the whole population. However, we do not necessarily recommend following this policy; we only quantify its costs.

4.5 CASE STUDY: HIV SIMULATION IN SUB-SAHARAN AFRICA

In this section, we use the large-scale HIV simulation model described in Section 3.5 to test the performance of allocation policies. This simulation model allows us to relax some of the ADP assumptions, such as the Markovian progression, and the fixed sequence of treatment phases.

4.5.1 Results

Our analysis indicates that the ADP policies indeed outperform the benchmark policies in terms of total and discounted total population. Table 6 shows the objective function improvement by our policy for each coverage level compared with WHO recommendations. As can be seen, the ADP policies outperform WHO recommendations by as much as 8%.

Table 6: Performance of policies compared to nonabandonment policy (%)

Coverage	15	28	47	58	67	84
Nonabandonment state-independent benchmark	-1.9	-3.1	-2.4	-4.2	-0.7	-4.3
Nonabandonment ADP	4.1	0.6	0.1	0.4	2.1	0.8
Abandonment-permitted state-independent benchmark	1.5	2.2	4.8	4.8	6.7	4.7
Abandonment-permitted ADP	4.8	2.9	7.2	7.1	8.2	6.2

4.5.2 Policy Insights

To gain insight into the ADP policies, we consider how ADP policies assign and remove patients from treatment. Since the ADP policy is state-dependent, we focus on two factors which are important for policy makers: prevalence, and coverage. We analyze the ADP policy in a variety of prevalence and coverage levels. Table 7 shows how the ADP policies assign treatment, where rows correspond to coverage levels and columns correspond to prevalence levels. We consider three categories for coverage and prevalence: low, medium, and high. As can be seen, both risk and health are important for assigning treatment. In most scenarios,

Table 7: Risk and health priorities in ADP assignment

Coverage \ Prevalence	Low [0,3%)	Medium [3%,7%)	High [7%,15%)
Low [0, 35%)	Poly>Mono>Child Moderate>Sick>Healthy	Poly>Child>Mono Sick>Healthy>Moderate	Poly>Mono>Child Moderate>Sick>Healthy
Medium [35, 70%)	Child>Poly>Mono Healthy>Moderate>Sick	Poly>Mono>Child Moderate>Healthy>Sick	Poly>Mono>Child Healthy>Moderate>Sick
High [70%, 100%)	Poly>Mono>Child Moderate>Healthy>Sick	Poly>Mono>Child Healthy>Sickest>Moderate	Poly>Child>Mono Moderate>Sick>Healthy

Note that Poly stands for polygamous and Mono stands for monogamous

polygamous patients have the highest priority for receiving treatment. The ADP policies then prioritize monogamous patients and finally children. In most scenarios, the ADP policies first prioritize patients having a moderate health state. Moreover, our analysis shows that risk is relatively more important than health. This result differs markedly from WHO recommendations, which prioritize the sickest patients and does not consider risk.

Table 8 provides details on the assignment procedure. The risk categories are shown in rows, and the health categories are shown in columns. Each entry in the table shows the ranking associated with the "risk-health" pair in the priority list of the ADP policy associated with the scenario for high prevalence and low coverage. We sum the priorities in each column to find an aggregate priority for each health category. Similarly, we calculate the aggregate priority for each risk category. Table 8 shows that health and risk are important in assigning treatment. In this scenario, polygamous patients have the highest priority in receiving treatment, then the monogamous patients and finally infected children. The ADP policy prioritizes patients with moderate health state, then the sickest and finally the healthiest patients. We also investigate when the ADP policies remove patients from treatment in a variety of prevalence and coverage levels. In contrast to nonabandonment policies, ADP policies mainly remove patients from treatment when their maximum CD4 reaches the highest health category. Loosely speaking, ADP policies stop treatment when CD4 count reaches 350 cells/mm^3 or starts declining. This result is observed in almost all coverage and prevalence levels. We also compare the mean treatment time for patients under each policy. Our

Table 8: Aggregated priorities for health and risk under the ADP policy

Risk	Health (CD4 categories) [0,50)	[50,100)	[100,200)	[200,350)	[350,∞)	Aggregated risk
0	20	24	21	23	18	106
1	22	8	16	15	25	86
3	11	14	5	19	17	66
5	4	3	10	9	12	38
7	6	13	1	2	7	29
Aggregated health	63	62	53	68	79	

results show that the mean treatment time for the ADP policies are almost 30% of the mean treatment time for WHO policies. Figure 8 shows the mean treatment time under WHO and ADP policies for different coverage levels. Moreover, we define "effective coverage" as the total proportion of the infected population who receive treatment at some point in their life; that is, the long-term proportion of the infected population who receive treatment. The ADP policies have the highest effective coverage, so that they treat a greater proportion of the infected population. Even in low coverage levels the ADP policies treat more than 85% of the infected population at some point. Since the number of available treatment doses has increased in Sub-Saharan Africa during the past decade, we consider a setting in which the number of treatment doses increases according to the trend of ART growth in Sub-Saharan Africa. We consider the initial coverage of 58% and test the performance of the ADP policies against the WHO recommendations via the HIV simulation model. Our analysis shows that the ADP policies outperform the WHO recommendations by 1%.

4.6 HIV TRANSMISSION DYNAMICS FORMULATION

In this section, we describe our transmission model which extends the transmission model used in Garnett and Anderson [1994]. They use a deterministic compartmental framework to describe the transmission dynamics. They model the dynamics of the system by using a

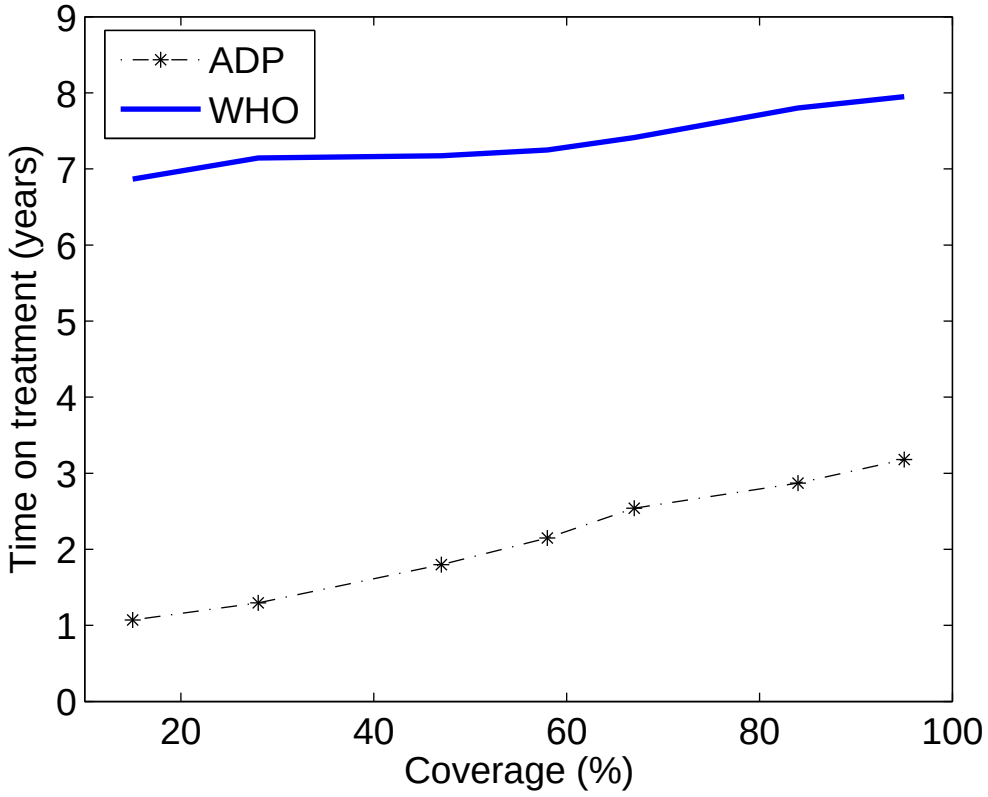


Figure 8: Comparison of treatment time under WHO and ADP policies

deterministic system of differential equations. In their model, the total number of susceptible individuals in risk group r who become infected in a period is calculated by

$$\nu X_r \sum_{r'} \omega_{r,r'} \frac{Y_{r'}}{N_{r'}},$$

where $Y_{r'}$ is the total number of infected individuals in risk group r', and ν denotes the transmission probability per partnership.

Fix a state $S \in \mathcal{S}$, and let $p_r(S, a)$ denote the probability of contagion of a susceptible individual in risk group r. Let $A_{r,n}$ denote the event that a susceptible individual in risk group r becomes infected in his/her n-th partnership, and let B_r denote the number of partnerships

established in a period which we assume has the distribution $q_r(n), \quad n = 0, 1, 2, \cdots L_r$. Therefore, we have

$$p_r(S,a) \quad = \quad 1 - \sum_{n=0}^{L_r} P(\bigcap_{m=1}^{n} A_{r,m}^c) q_r(n) = 1 - \sum_{n=0}^{L_r} (1 - \psi_r(S,a))^n q_r(n),$$

where we assume that the events $A_{r,m}$ are independent and equally likely, and $\psi_r(S,a)$ denotes the probability that a random partnership results in infection of a susceptible individual with risk r. Following Garnett and Anderson [1994] one has that (in the setting where policy makers may remove patients from treatment)

$$\psi_r(S,a) = \sum_{r' \in R} \omega_{rr'} \frac{\sum_{h,p} \nu_{r',h,p} \ (Y_{r',h,p} + a_{r',h,p} - a_{r',h,p+1})}{N_{r'}},$$

where $\omega_{rr'}$ is the probability that a susceptible individual of risk r forms a partnership with someone of risk r', and the term $\sum_{h,p}(Y_{r',h,p}+a_{r',h,p}-a_{r',h,p+1})/N_{r'}$ represents the probability that a partnership is established with an infected patient after taking the action, conditional on such a partner having risk r'. Note that $\nu_{r',h,p}$, the probability of transmission in a partnership, depends on the risk group r', health state h, and treatment phase p of the infected partner.

By using the Taylor series expansion of $(1 - \psi_r)^n$ we have (suppressing S and a for simplicity)

$$(1 - \psi_r)^n \approx 1 - n\psi_r + \mathcal{O}(\psi_r^2 \frac{n(n-1)}{2}), \tag{4.9}$$

where $\mathcal{O}$ denotes the error order for this approximation. By using (4.9) we approximate $p_r(S,a)$ by $\hat{p}_r(S,a)$. Therefore, we have

$$\hat{p}_r(S,a) = 1 - \sum_{n=0}^{L_r} (1 - n\psi_r) q_r(n) = \mu_r \psi_r(S,a), \tag{4.10}$$

where

$$\|p_r(S,a) - \hat{p}_r(S,a)\| \leq \frac{\psi_r^2}{2} \left[Var(n) + \mu_r^2 - \mu_r \right].$$

In our setting, $\psi_r < 0.01$ and $\mu_r < 10$, and the maximum error is relatively small.

The partnership patterns among activity groups can be described by mixing matrices. Define $\Omega = [\omega_{rr'}]$ as a mixing matrix where $\omega_{rr'}$ is the probability that a person in risk group r forms a partnership with another person in risk group r'. The structure of this matrix

determines the mixing patterns. Two extreme cases are assortative and disassortative mixing. In assortative case, individuals in the same risk group form partnerships together and in the disassortative case, individuals tend to form partnerships with other risk groups. Between these two extreme cases, there is also random mixing in which the probabilities in the matrix is proportional to the total supply of sexual partnerships of risk group r. In other words, in random mixing we have $\omega_{rr'} = \frac{N_{r'}c_{r'}}{\sum_{r''} N_{r''}c_{r''}}$, where N_r is the total number of individuals in risk group r, and c_r is the mean number of partnerships an individual forms in a period. In our study we use a mixing pattern which is common in mathematical studies of STDs. Let $\Delta = [\delta_{rr'}]$ be the identity matrix and θ be the degree of assortative mixing. We use the following mixing pattern

$$\omega_{rr'} = (1-\theta)\delta_{rr'} + \theta\big(\frac{N_{r'}c_{r'}}{\sum_{r''} N_{r''}c_{r''}}\big).$$

This approach is suitable for numeric simulations and can capture many different mixing scenarios [Garnett and Anderson, 1994]. We set $\theta = 0.7$ as our base case.

4.7 SAMPLING CONSTRAINTS

Regarding the selection of c, one can show that minimizing (4.8) is equivalent to minimizing

$$\sum_{S\in\mathcal{S}} \frac{c(S)}{|S|+1}\left|\hat{V}_\alpha(S) - V(S)\right|.$$

As noted by de Farias and Van Roy [2004], c regulates the quality of the approximation across $\mathcal{S}$, and can therefore be used to target certain regions of the state space where one aims to obtain better approximations. In that regard, we would like to obtain better approximations in the states that are most likely to be visited in the near future when the *optimal policy* is used. For a policy π, define the distribution c_π by

$$c_\pi(S) := (1-\lambda)\sum_{t=0}^{\infty} \lambda^t \mathbb{P}_\pi\left\{S^t = S | S^0\right\}, \quad S \in \mathcal{S},$$

where S^0 is an initial state representative of the current population, and λ is the discount factor. We would like to use c_{π^*} in the objective function of (4.8), and also in sampling

$\overline{\mathcal{S}}$ through ψ, as prescribed in de Farias and Van Roy [2004, Theorem 3.1., p.469]. Unfortunately, one does not have prior access to π^*. Let π^0 denote an initial allocation policy. Finding c_{π^0} is computationally intractable, thus, we settle for approximating it using its empirical counterpart, $\hat{c}_{\pi^0,T}$, which is given by

$$\hat{c}_{\pi,T}(S) := (1-\lambda)\sum_{t=0}^{T}\lambda^t \mathbf{1}_{\{S^t(\omega)=S\}}, \quad S \in \mathcal{S},$$

where $\{S^t(\omega) : t \geq 0\}$ represents the outcome of a simulation, and $T > m$ denotes the simulation budget.[6] We use this simulation run to select $\overline{\mathcal{S}}$ as well: computing ψ is infeasible, thus we approximate it as $\hat{c}_{\pi,T}$. Note that the underlying motivation is that on most simulation runs, states are visited at most once, thus we approximate $\mathbb{P}_\pi\{S^t = S | S^0 = S'\} \approx \sum_{n=1}^{N} \mathbf{1}_{\{S^t(\omega_n)=S\}}/N$, where N is the number of replications. This results in $\psi \approx c$.

4.8 CONCLUSIONS

This chapter quantifies the price of following nonabandonment policies in HIV treatment in resource-limited settings. First, we develop a Markov decision process model to optimize the allocation of scarce HIV treatment for a broad class of admissible policies. Then, we consider two classes of admissible policies: (i) nonabandonment, and (ii) abandonment-permitted. The price of nonabandonment is the difference between the optimal solutions of the above settings. Since the MDP formulation has unbounded state space for each problem, we estimate a lower bound for the price of nonabandonment by the difference between a lower bound on the performance in the abandonment-permitted setting and an upper bound of that in the nonabandonment setting. We use the linear programming approach to approximate dynamic programming to develop an algorithmic approach to find an efficient allocation policy. By providing upper bounds for our approximations we show that the policies produced by our method are close to optimal. Our results show that the price of following the nonabandonment policies is as much as 41% of the total discounted QALYs of

[6] In our numerical study we take the average over many replications.

the whole population. We compare the performance of proposed policies with WHO recommendations via the simulation model. Our results show that the ADP policies outperform WHO recommendations by as much as 8%. Regarding the structure of the ADP policy, we analyze how it prioritizes patients for initiating treatment and when it removes patients from treatment in a variety of scenarios. In assigning treatment, both risk and health status are important, but risk is relatively more important than health. In particular, the ADP policies in most scenarios prioritize polygamous patients, then monogamous and finally children. The ADP policies mostly prioritize patients with moderate health state. In removing patients from treatment, the ADP polices remove patients whose maximum CD4 count on treatment reaches the best health state. By removing patients from treatment policy makers can treat a greater proportion of the population which results in more QALYs for the whole population.

5.0 THE EFFECT OF PIPELINE DRUGS ON HIV TREATMENT

5.1 INTRODUCTION

The decision of when to start HIV therapy is an important clinical decision that remains controversial. Because timing decisions are not amenable to randomized controlled trials, this problem has been widely modeled and discussed in published reports [Braithwaite et al., 2008, Harrington and Carpenter, 2000, Ho, 1995, Holmberg et al., 2004, Lane and Neaton, 2003, Shechter et al., 2008]. These models generally seek to identify clinical conditions under which a patient should initiate ART so as to maximize his/her quality-adjusted life expectancy. They consider many factors, such as the initial viral load and CD4 count, age, gender, CD4 threshold and viral load threshold for initiating drugs, adherence, resistance, and HIV mutations at baseline. However, these models have not considered the rate of development of new antiretroviral drugs, assuming a fixed number of antiretroviral drugs assigned to a fixed number of distinct mechanistic categories. However, these numbers are unlikely to remain fixed over the time horizon of the model. We develop a model to address how treatment recommendations regarding when to start, switch, and sequence ARV regimens, would change with varying assumptions regarding the rates of new drug development, the proportion of new drugs in existing classes versus new mechanistic classes, the patterns of cross-resistance between new and existing mechanistic classes, and the toxicity of new drugs compared to existing drugs either in the same class or in a new class.

5.2 METHODS

We use the HIV simulation model of Braithwaite et al. [2008] to evaluate the outcomes of patients treated under different assumptions about the availability and characteristics of new antiretroviral drugs. The Braithwaite model is an individual microsimulation that replicates the individual progression of disease (CD4 counts, viral loads, presence of mutations, treatment status, etc.) and estimates HIV-related mortality as a function of those individual patient characteristics [Braithwaite et al., 2005]. It incorporates baseline mortality, HIV-related mortality and the toxicity of ARVs. A notable aspect of the model is the mechanistic manner by which it represents the development of HIV antiviral resistance [Braithwaite et al., 2005, 2006]. It can predict the time to treatment failure, survival, and the development of HIV antiviral resistance [Braithwaite et al., 2005, 2006]. We modify it by incorporating the arrival of new drugs, those within existing classes of drugs and the development of new classes of antiretroviral agents. This allows the simulation to treat patients with more cycles of therapy, and provides increased flexibility for changing to a different drug combination after the development of resistance.

In our base case, we simulate a cohort of patients treated under the assumption of the availability of three classes of antiretroviral drugs, without the future development of new drugs, which is a common assumption used by most HIV treatment models. We compare the life expectancy and quality-adjusted life expectancy of an identical cohort treated under multiple scenarios assuming the future development of new drugs within existing classes and for new classes. We estimate the optimal criteria for the initiation of ARV in the presence of pipeline drugs. Because of considerable uncertainty regarding variability in the effectiveness and toxicity of new drugs, we explore a wide variety of assumptions. Based on historical data, we empirically estimate 1) the probabilistic arrival of HIV pipeline drugs for both current and brand new classes of drugs, and 2) the likelihood of cross-resistance between new and existing mechanistic classes.

5.2.1 Analyzing Inter-Arrival Time of Pipeline Drugs

We fit the probability distribution for the inter-arrival times of new drugs, defined as when the drug was approved by the Food and Drug Administration (FDA), to an exponential distribution with rate λ using data from the FDA database [Food and Drug Administration, 2010]. The parameters of distributions are estimated by the maximum likelihood estimator (MLE) technique. Goodness-of-fit is tested by Quantile-Quantile plot and Kolmogorov-Smirnov tests [Montgomery et al., 2003]. The statistical programming language "R" was used for all estimates and statistical tests. We model the arrival of pipeline drugs as a Poisson process. If the overall arrival process is a Poisson process with rate Λ, ie, $PP(\Lambda)$, then, if the arrival is of type i with probability p_i, independent of everything else, then the i^{th} process is $PP(\Lambda p_i)$. This is referred to as splitting a Poisson process [Nelson, 1995]. We assume that drug types split to new classes and existing classes according to a Bernoulli splitting mechanism. Therefore, the arrival of new classes and new drugs belonging to existing classes is also a Poisson process. Moreover, if a new drug belonging to an existing class arrives, we assume that it will be uniformly distributed among current classes. A schematic view is shown in Figure 9.

5.2.2 Cross-Resistance

The development of HIV antiviral resistance is complex, and mutations in the HIV genome that confer resistance to a particular drug may also confer partial resistance to other drugs, a phenomenon known as cross-resistance. Since cross-resistance will likely plague new drugs as it does existing ones, we include the possibility of developing cross-resistance in new drugs as well. Cross-resistance is substantially more likely in drugs within the same class than between drugs of a different class [Johnson et al., 2010]. More specifically, mutations in the nucleoside reverse-transcriptase inhibitors (NRTI) and non-nucleoside reverse-transcriptase inhibitors (NNRTI) class are both in the Reverse Transcriptase gene, but there is no mutual mutation among drugs in these classes, so these is no cross-resistance pattern among drugs in the NRTI and NNRTI classes. Since mutations in the protease inhibitors (PI) class occur

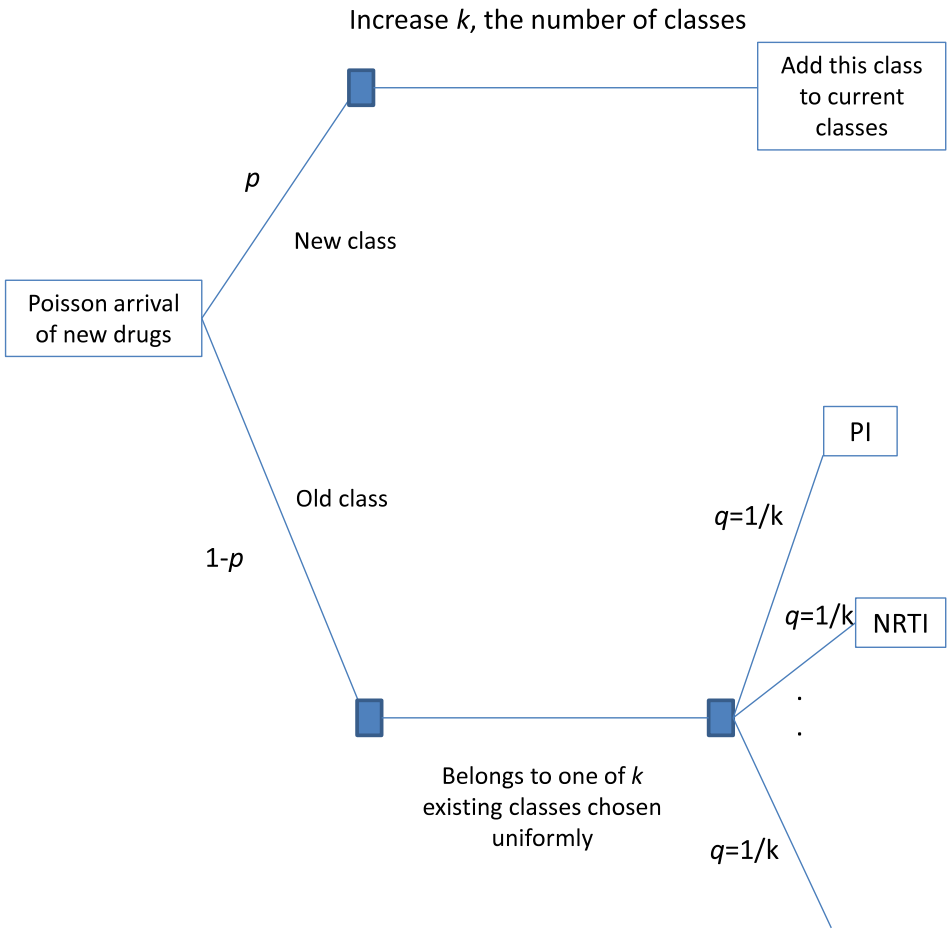


Figure 9: The arrival process of HIV pipeline drugs

in the Protease gene and in the NRTI and NNRTI class occur in Reverse Transcriptase gene [Johnson et al., 2010], there is no cross-resistance among drugs in these classes. Therefore, we assume that there is no development of cross-resistance between classes of drugs.

We model the probability distribution of cross-resistance pattern in each drug class. The cross-resistance of new drugs is assumed to be equal to the cross-resistance probability

distributions of existing drugs, i.e., if a new drug belongs to the NRTI class, it will follow the resistance pattern of the NRTI class. The probability that a specific mutation will confer resistance to a new drug is estimated by the proportion of drugs in that class for which the mutation is known for conferring resistance. First, we find the total number of drugs for which a particular mutation confers resistance. For example, in the NRTI class, the M41 mutation confers resistance only to Stavudine and Zidovudine, so the total number of drugs for which M41 confers resistance is 2 [Johnson et al., 2010]. This procedure is repeated for all mutations in each class. Then, the best probability distribution is fit to the number of drugs for which each mutation confers a resistance. To determine the cross-resistance probability in each class, we generate a random variate from the distribution and then divide it by the total number of drugs in that class. We assume that mutations are independent and equally likely to happen. We separate the mutations into two groups of major and minor mutations and for each group we find the best probability distribution of number of drugs resistant to that kind.

5.2.3 Efficacy and Toxicity of New Antiretroviral Agents

The efficacy of a particular drug is represented by its ability to decrease viral load. For the base case, we assume that the viral load decrement of new drugs is equal to the average of viral load decrements of drugs in the same class. The Braithwaite model assumes that the toxicity of all classes of drugs is the same [Braithwaite et al., 2008], we also assume that toxicity of new drugs will also be the same and equal to the previous toxicity level. In the sensitivity analysis, we test scenarios in which the efficacy and toxicity of pipeline drugs are different from existing drugs.

5.2.4 Scenarios Regarding When to Initiate ART

Successive populations of individuals with newly diagnosed chronic HIV infection were considered, each of them starting with CD4 count of 500 cells/mm^3. We consider CD4 thresholds starting from 50 cells/mm^3 until 500 cells/mm^3 with increments of 50 cells/mm^3, which are consistent with current guidelines [Braithwaite et al., 2008]. In addition, different starting

age categories (30, 40, and 50) and baseline viral loads of 10^4, $10^{4.5}$, 10^5 and $10^{5.5}$ copies/mL are modeled. Mean life-years and mean quality-adjusted life-years are calculated for policy making comparisons. In each category, the optimal CD4 count threshold for treatment initiation is found. For each of these thresholds, the life expectancy is calculated and the threshold with the maximum life expectancy is chosen as the optimal time for initiating the therapy for each category.

5.2.5 Scenarios Regarding Sensitivity Analysis

We vary several model parameters to assess the impact on model predictions of the effect of pipeline drugs on population survival. Specifically, we vary the inter-arrival time of new drugs (all varied across 95% confidence limits of our estimates), the rate at which new drugs accumulate mutations, the level of adherence across drugs, the effectiveness of new pipeline drugs compared to existing drugs, and the toxicity level of new drugs. In scenarios where the efficacy of the new drug is equivalent to the average of the existing drugs, the new drug is added as an extra regimen when the patient has exhausted all existing regimens. However, in sensitivity analysis where the new drug is better than existing drugs, we assume the new drug is used after the first regimen has failed.

5.3 RESULTS

5.3.1 Probability Distributions

Table 9 shows the estimated parameter values for the exponential distributions, i.e., λ, and the respective p-values indicating whether we reject the null hypothesis that the observed distribution is an exponential distribution with rate parameter λ. The distribution of inter-arrival times of drugs is exponential with mean $\frac{1}{\lambda} = 7.69$ months, which implies that the arrival of new drugs follows a Poisson process with rate $\lambda = 0.13$. The Quantile-Quantile plot for this fit is shown in Figure 10. The arrival process of a new drug is assumed to follow

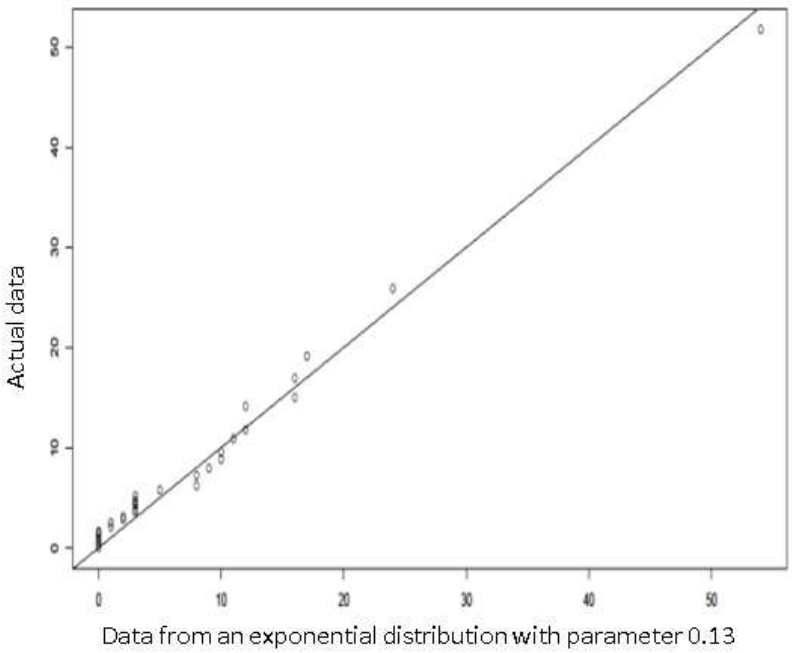


Figure 10: Quantile-Quantile plot for the goodness of fit for the arrival process

a split Poisson process [Nelson, 1995]. If a drug arrives, it will be from a new class with probability p, and from current classes with probability $(1-p)$. Using the point estimate method we have $p = \frac{6}{31}$. Using this estimate, the probability distributions and the p-values for Kolmogorov-Smirnov goodness of fit test associated with these distributions are calculated and shown in Table 9.

If the population distribution is exponential, it can be shown that the $100(1-\alpha)\%$ confidence interval for λ from a sample of $X_1, X_2, \cdots, X_n$ is

$$(\chi^2_{2n;\frac{\alpha}{2}})/(2n\overline{X}) < \lambda < (\chi^2_{2n;1-\frac{\alpha}{2}})/(2n\overline{X}),$$

where $\overline{X}$ is the mean of the sample and χ^2_{2n} is a Chi-square distribution with $2n$ degrees of freedom and $Pr(\chi^2_{2n} > \chi^2_{2n;\frac{\alpha}{2}}) = \frac{\alpha}{2}$ [Montgomery et al., 2003]. A 95% confidence interval for inter-arrival times of each distribution is reported in Table 9.

Table 9: Validity of exponential inter-arrival time distributions

	Probability distribution	p-value	95% CI
Inter-arrival time of new drugs	Exp ($\lambda = 0.13$)	0.085	[0.09,0.181]
Inter-arrival time of new classes	Exp ($\lambda = 0.02$)	0.725	[0.006,0.041]
Inter-arrival time of new drugs belonging to existing classes	Exp ($\lambda = 0.104$)	0.112	[0.068,0.147]

Table 10: Approval date of ARV classes

Drug Class	Date of approval of the first drug
NRTI	March 1987
PI	Dec 1995
NNRTI	June 1996
Fusion Inhibitor	March 2003
Integrase Inhibitor	October 2007
Entry Inhibitor	August 2007

Table 11: The cross-resistance probability distributions

Drug Class	Number of drugs	Probability distribution of number of drugs resistant to a mutation	p-value
NRTI	7	Uniform$[1, 4]$	0.059
NNRTI	3	Uniform$[1, 3]$	0.042
PI	8	Poisson($\lambda = 3$)	0.024

First, we test the assumption that if a new drug belonging to an existing class arrives, it will be uniformly distributed among them. The approval date of the first drug in each class is shown in Table 10 [Food and Drug Administration, 2010]. Between Dec 1995 and June 1996, when there were only two classes of drugs, two drugs were approved from the PI class.

Table 12: The probability distribution of the number of drugs resistant to a mutation

Class	Probability distribution				Number of mutations	
	Major	p-value	Minor	p-value	Major	Minor
NRTI	Uniform$[1, 4]$	0.059	N/A	N/A	8	N/A
NNRTI	Poisson$(\lambda = 2.44)$	0.037	1	N/A	9	5
PI	Poisson$(\lambda = 3.25)$	0.722	Poisson$(\lambda = 2.88)$	0.025	12	26

Assuming the uniform distribution, this event happens with probability 0.25. Between June 1996 and March 2003, when there were three classes of drugs, 11 drugs were approved from which four belong to the PI class, five belong to the NRTI class and two belong to the NNRTI class. We fit the uniform distribution to this data and the corresponding p-value is 0.08253. Therefore, when we had two or three classes of drugs, the new drug was equally likely from current classes in hand, supporting the assumption that new drugs are distributed equally among existing classes.

The cross-resistance probability distributions are shown in Table 11 [Johnson et al., 2010]. The best fitting distributions for the probability of cross-resistance within NRTIs and NNRTIs are uniform; the probability of cross-resistance in the PIs is Poisson. For the other three classes of new drugs (Fusion Inhibitors, Entry Inhibitors and Integrase Inhibitors) no distribution can be fit since there is only one drug in each class by 2011.

Drugs in the NRTI class are divided into two groups, thymidine-associated mutations (TAMs) and non-thymidine-associated mutations (Non-TAMs). Stavudine and Zidovudine are TAMs and the other five are Non-TAMs. Two of ten existing mutations confer resistance to both TAMs and Non-TAMs [Johnson et al., 2010], so the cross-resistance probability is estimated to be 0.2 between TAMs and Non-TAMs. We differentiate between TAMs and Non-TAMs for making the new regimens. The probability distribution of the number of drugs resistant to a major or minor mutation is shown in Table 12.

Table 13 shows life-years and QALYs of patients in the base model for different age, VL, and starting CD4 count categories. Table 14 presents the relative gain of life-years and QALYs of identical cohorts simulated under conditions of no new pipeline drugs compared to simulation with the stochastic arrival of new antiretroviral agents. The relative life-year

gain less than 0.01 % is considered to be zero. Across all ages, viral loads and CD4 counts at initiation of therapy, the life-year gain is at most 2% and in some scenarios this gain is near zero. Table 15 shows the optimal CD4 count threshold for initiating the therapy for each scenario for both the validated simulation model and the simulation model with the inclusion of pipeline drugs.

Table 13: Life-years and QALYs

		CD4 threshold=200		CD4 threshold=350		CD4 threshold=500	
Age 30 years		Life years	QALYs	Life years	QALYs	Life years	QALYs
Viral Load	$10^{4.0}$	37.561	33.079	38.637	33.913	38.958	33.969
	$10^{4.5}$	37.016	32.356	38.579	33.651	38.917	33.766
	$10^{5.0}$	36.695	31.824	38.18	33.109	38.752	33.441
	$10^{5.5}$	35.465	30.48	36.978	31.764	37.51	32.096
Age 40 years							
Viral Load	$10^{4.0}$	29.247	25.924	30.043	26.544	30.195	26.473
	$10^{4.5}$	28.638	25.214	29.775	26.162	30.318	26.467
	$10^{5.0}$	28.685	25.067	29.807	26.043	30.207	26.248
	$10^{5.5}$	28.269	24.499	29.261	25.345	29.624	25.538
Age 50 years							
Viral Load	$10^{4.0}$	21.445	19.147	21.902	19.47	21.933	19.319
	$10^{4.5}$	20.794	18.451	21.667	19.167	21.753	19.102
	$10^{5.0}$	20.752	18.299	21.797	19.187	21.881	19.133
	$10^{5.5}$	20.71	18.125	21.574	18.856	21.809	18.951

5.3.2 Sensitivity Analysis

The result of the analysis is reported in Tables 16, 17, and 18. Numbers in the table show the gain in QALYs (in percent) by using the pipeline drugs. In the sensitivity analysis, we initiate

Table 14: Relative life-years and QALYs gain due to pipeline (%)

		CD4 threshold=200		CD4 threshold=350		CD4 threshold=500	
Age 30 years		Life years	QALYs	Life years	QALYs	Life years	QALYs
Viral Load	$10^{4.0}$	0.00	1.14	0.37	1.75	0.00	1.62
	$10^{4.5}$	0.58	2.24	0.14	2.01	0.00	1.92
	$10^{5.0}$	1.06	3.32	1.23	3.58	0.11	2.62
	$10^{5.5}$	4.53	7.65	3.99	7.26	3.29	6.63
Age 40 years							
Viral Load	$10^{4.0}$	0.00	0.24	0.00	0.86	0.19	1.28
	$10^{4.5}$	0.00	0.94	0.43	1.70	0.19	1.28
	$10^{5.0}$	0.24	1.88	0.44	1.86	0.19	1.58
	$10^{5.5}$	2.27	4.59	2.40	4.86	1.82	4.40
Age 50 years							
Viral Load	$10^{4.0}$	0.00	0.00	0.00	0.05	0.00	0.21
	$10^{4.5}$	0.00	0.11	0.78	1.55	0.86	1.79
	$10^{5.0}$	0.48	1.47	0.78	1.55	0.86	1.79
	$10^{5.5}$	1.79	3.33	0.78	2.08	0.86	2.01

treatment at CD4 count of 350 cells/mm^3. The sensitivity analysis indicates that varying the estimates of the inter-arrival times of new drugs, the rate of accumulation of resistance, the patient's adherence to treatment regimens, and the relative efficacy of pipeline drugs have little effect on overall outcomes, but that the toxicity of pipeline drugs has a potentially large effect on life expectancy. If the toxicity of pipeline drugs is reduced compared to existing drugs (the pipeline drugs have a mortality relative risk of 1), the presence of new pipeline drugs can increase the quality adjusted survival by as much as 13% in young patients with high viral load.

Table 15: The optimal CD4 count for initiating the therapy with and without pipeline

	Age categories					
	30 years		40 years		50 years	
VL	Base	Pipeline	Base	Pipeline	Base	Pipeline
4.0	450	450	450	450	300	450
4.5	450	450	450	450	450	450
5.0	450	450	450	450	450	450
5.5	450	450	450	450	450	450

Table 16: Sensitivity analysis for 30 year old patients

				VL		
				4.5	5.0	5.5
	Low	Base	High			
Inter-arrival time	0.09	0.13	0.181	(1.75,2.01,2.02)	(3.13,3.58,3.86)	(6.84,7.26,7.47)
Rate mutations	0.16	0.18	0.2	(2.01,2.01,1.94)	(3.59,3.58,2.95)	(7.29,7.26,7.24)
Adherence	0.62	0.75	0.76	(1.08,2.01,2.01)	(2.51,3.58,3.58)	(6.08,7.26,7.26)
viral load decrement	-1	0	1	(1.88,2.01,2.02)	(3.58,3.58,3.58)	(7.25,7.26,7.36)
Toxicity	1	1.5	1.7	(4.19,2.01,1.01)	(7.41,3.58,2.34)	(13.03,7.26,5.66)

Table 17: Sensitivity analysis for 40 year old patients

				VL		
				4.5	5.0	5.5
	Low	Base	High			
Inter-arrival time	0.09	0.13	0.181	(1.13,1.70,1.70)	(1.86,1.86,2.58)	(4.13,4.86,4.87)
Rate of mutations	0.16	0.18	0.2	(1.70,1.70,1.70)	(1.86,1.86,1.86)	(4.32,4.86,4.73)
Adherence	0.62	0.75	0.76	(1.00,1.70,1.70)	(1.16,1.86,1.95)	(3.52,4.86,4.86)
Viral load decrement	-1	0	1	(1.60,1.70,1.70)	(1.86,1.86,1.94)	(4.58,4.86,4.86)
Toxicity	1	1.5	1.7	(3.78,1.70,0.73)	(5.15,1.86,1.09)	(9.47,4.86,3.04)

5.4 DISCUSSION

Models with and without the inclusion of pipeline drugs support a similar policy for initiating the therapy considering either life expectancy or quality-adjusted life expectancy. Consis-

Table 18: Sensitivity analysis for 50 year old patients

				VL		
				4.5	5.0	5.5
	Low	Base	High			
Inter-arrival time	0.09	0.13	0.181	(0.83,1.55,0.71)	(0.69,1.55,1.55)	(1.86,2.08,2.18)
Rate of mutations	0.16	0.18	0.2	(1.55,1.55,0.97)	(1.55,1.55,0.78)	(2.57,2.08,1.75)
Adherence	0.62	0.75	0.76	(0.44,1.55,1.55)	(0.30,1.55,1.55)	(1.40,2.08,2.08)
Viral load decrement	-1	0	1	(1.55,1.55,1.55)	(1.43,1.55,1.55)	(2.08,2.08,2.56)
Toxicity	1	1.5	1.7	(1.98,1.55,1.04)	(1.94,1.55,0.45)	(5.78,2.08,1.78)

tent with current treatment recommendations, the base case model (that does not include the availability of pipeline drugs) supports early treatment in most scenarios. In virtually all scenarios, the model that includes the availability of pipeline drugs supports initiating therapy at CD4 level of 500 cells/mm^3. The quality-adjusted life expectancy gain from the inclusion of pipeline drugs in all categories ranges from no gain to almost 8%. This translates to almost 2.3 years of additional quality-adjusted life expectancy for a hypothetical healthy 30 year old HIV-infected patient with a VL of $10^{5.5}$, and therapy initiated at the CD4 count of 350 cells/mm^3.

We find that the optimal time to initiate the therapy for HIV is sensitive to the existence of pipeline drugs. This result is intuitive, as one expects the availability of more drugs would prompt earlier initiation of therapy and switching between drugs more frequently. However, the overall impact of new drugs is not large, primarily because there are already enough regimens available. The base simulation model is calibrated for resource-rich environments and in its current version, 17 drugs exist which might be interpreted as enough drugs for HIV treatment in resource-rich environments. In the model, a patient remains on the last regimen even if she has accrued resistance to that regimen and accrues some benefits from the last regimen, although less than prior to becoming resistant to it. Imposing this assumption is also biased against the effect of pipeline drugs.

This study has several limitations. Our data are from a cohort that is overwhelmingly male, and thus our results may not apply to women. For policy recommendations, cost has not been considered, which may have impact on policy recommendations. Our model does

not include spreading of resistance patterns in the native viral population. As resistance spreads, some newly infected individuals are infected with already resistant strains.

Toxicity of new pipeline drugs is the most important factor for improving the outcomes of ARV. This finding is based on the assumption that there is currently a small but real toxicity to existing HIV medications, which is supported in the literature but for which the exact magnitude is not precisely known. The improvement of QALYs can be as high as 13% in scenarios where pipeline drugs are not toxic. Therefore, the effort to make the new HIV drugs less toxic should be considered as the highest priority.

6.0 CONCLUSIONS

This dissertation applies mathematical models to address fundamental questions in HIV treatment. Containing HIV is a primary global health issue and managing scarce HIV treatment is a top priority. Antiretroviral drugs are the only treatment option for chronic HIV infection and demand for them far exceeds the supply in resource-limited settings. The area hit hardest by the HIV epidemic is Sub-Saharan Africa, where the majority of countries have coverage levels of less than 50%. In Chapter 3, we developed a simulation model to measure the effect of HIV treatment on the infected population size and the quantity of treatment doses needed to treat a proportion of the infected population. In developing the simulation of an infected population, we used an individual simulation model calibrated with data from Kenya. We showed that coverage is not a static concept, and the conventional way of thinking about coverage is not sufficient to describe the effect of treatment on the population. This fact is a direct consequence of the treatment effect on patients' lives. We introduced cumulative incidence-based coverage as the long run proportion of infected patients who receive treatment in their life time. We showed that this new definition is capable of capturing the effect of population growth on the resources needed to treat the population. Our results show that to reach the goal of international organizations of covering most of infected patients in Sub-Saharan Africa, we need substantially more resources than what have been predicted.

For resource-limited settings, WHO guidelines recommend treating the sickest patients in the population and treating them until death. HIV-infected patients who are on treatment develop resistant mutations and treatment is marginally effective for them. Treating patients until death hinders the opportunity of reallocating treatment to other patients who might benefit more. In Chapter 4, we quantified the price of following the nonabandonment policies

in HIV treatment in resource-limited settings. We proposed a mathematical model to find efficient allocation of scarce HIV treatment for a broad class of admissible policies. Then, for quantifying the price of nonabandonment policies we restricted our attention to two classes of admissible policies: (i) nonabandonment, and (ii) abandonment-permitted. Solving the allocation problem for each class of admissible policy is intractable since the state space is unbounded. Therefore, we estimated a lower bound on the price of nonabandonment policies by the difference between a lower bound on the performance in the abandonment-permitted setting and an upper bound of that for the nonabandonment setting. For finding the lower bound we provided an algorithmic approach based on the linear programming approach to approximate dynamic programming. We showed that the optimal policy of the approximation problem is state-dependent priority-rule. We provided two techniques to compute the upper bound. The first one is based on the relaxation of our problem and the second one is a natural bound from ADP. By providing upper bounds for our approximations we showed that the policies produced by our algorithmic approach are near optimal. Our results show that the price of nonabandonment policies is as much as 41% of the total discounted QALYs of the whole population. We also analyzed the optimal ADP policy to derive insights on how they assign treatment and remove patients from treatment in a variety of settings. Our results show that both risk and health are important in assigning treatment. In particular, risk is relatively more important than health. The ADP policies prioritize polygamous patients, then monogamous and finally children in assigning treatment. Moreover, the ADP policies prioritize patients with moderate health state in most scenarios. In removing patients from treatment, the ADP policies remove patients from treatment when the maximum CD4 count reaches the best health category. By removing patients from treatment a larger proportion of the infected population can be treated, resulting in more QALYs for the whole population. We used the large-scale HIV simulation model to test the performance of allocation policies. Our results show that the ADP policies outperform WHO recommendations by as much as 8%.

When to start HIV treatment is a fundamental question in the HIV literature. Available models assume a fixed number of available treatment doses and do not consider the rate of new antiretroviral development on optimal timing of HIV treatment. In Chapter 5, we

investigated the effect of pipeline drugs on HIV treatment in resource-rich settings. We used a split Poisson process to model the arrival of HIV pipeline drugs. Then, we used data on pipeline drugs approved by the Food and Drug Administration to calibrate our model. We incorporated the arrival of HIV pipeline drugs into the validated HIV simulation model to analyze the effect of pipeline drugs on: (i) the optimal time to initiate treatment, and (ii) QALYs of patients. Our model with the inclusion of pipeline drugs supports earlier treatment strategies. In particular, it supports initiating HIV treatment at the CD4 count of 500 cells/mm^3. Our results show that considering pipeline drugs can increase the QALYs of patients by as much as 8%. Moreover, our sensitivity analysis shows that reducing the toxicity of pipeline drugs can increase the QALYs of patients by 13%. Therefore, for designing new antiretroviral drugs, reducing the toxicity should be the first priority.

Limitations of this work lie both on modeling assumptions and data. For instance, in Chapter 3, we assumed that the rate of new infections to the population is constant and independent of treatment. It is well established in the HIV literature that treatment reduces infectivity by reducing the viral load of patients. We will consider the effect of treatment on transmission in the future work. In Chapter 4, we assumed that policy makers have constant treatment doses at the beginning of each period. However, in Sub-Saharan Africa the number of treatment doses has increased during the past decade. We plan to extend our model to consider a dynamic environment where resources are a function of time. A primary data challenge in Chapter 4 is to find the probability that an individual changes his risk category in a period. In addition, the distribution over the risk groups is not known. While some assumptions and data are not comprehensive enough to solve our models, they provide a methodological framework for insights into these vexing questions.

BIBLIOGRAPHY

R.M. Anderson and R.M. May. *Infectious Diseases of Humans: Dynamics and Control*. Science Publications, Oxford, 1991.

M. Badri, S. Cleary, G. Maartens, J. Pitt, L.G. Bekker, C. Orrell, and R. Wood. When to initiate highly active antiretroviral therapy in Sub-Saharan Africa? A South African cost-effectiveness study. *Antiviral Therapy*, 11(1):63–72, 2006.

R.F. Baggaley, N.M. Ferguson, and G.P. Garnett. The epidemiological impact of antiretroviral use predicted by mathematical models: A review. *Emerging Themes in Epidemiology*, 2(9):doi: 10.1186/1742–7622–2–9, 2005.

S.E. Bellan, K.J. Fiorella, D.Y. Melesse, W.M. Getz, B.G. Williams, and J. Dushoff. Extracouple HIV transmission in Sub-Saharan Africa: A mathematical modelling study of survey data. *The Lancet*, 6736(12):61960–61966, 2013.

D. Bertsimas, V. Farias, and N. Trichakis. Fairness, efficiency and flexibility in organ allocation for kidney transplantation, 2013. Forthcoming in *Operations Research*.

S. Blower, L. Ma, P. Farmer, and S. Koenig. Predicting the impact of antiretrovirals in resource-poor settings: Preventing HIV infections whilst controlling drug resistance. *Current Drug Targets-Infectious Disorders*, 3(4):345–353, 2003.

R.S. Braithwaite, M.S. Roberts, C.H. Chang, M.B. Goetz, C.L. Gibert, M.C. Barradas, S.M. Shechter, A.J. Schaefer, K. Nucifora, R.T. Koppenhaver, and A.C. Justice. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: A decision model. *Annals of Internal Medicine*, 148(3):178–185, 2008.

R.S. Braithwaite, A.C. Justice, C.C.H. Chang, J.S. Fusco, S.R. Raffanti, J.B. Wong, and M.S. Roberts. Estimating the proportion of patients infected with human immunodeficiency virus who will die of comorbid disease. *American Journal of Medicine*, 118(8):890–898, 2005.

R.S. Braithwaite, S.M. Shechter, M.S. Roberts, A.J. Schaefer, D.R. Bangsberg, P.R. Harrigan, and A.C. Justice. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. *Journal of Antimicrobial Chemotherapy*, 58 (5):1036–1043, 2006.

R.S. Braithwaite, A.C. Justice, S.M. Shechter, A.J. Schaefer, J.B. Wong, and M.S. Roberts. Estimating the rate of accumulating drug resistance mutations in the HIV genome. *Value in Health*, 10(3):204–213, 2007.

R.S. Braithwaite, K.A. Nucifora, C.T. Yiannoutsos, B. Musick, S. Kimaiyo, L. Diero, M.C. Bacon, and K. Wools-Kaloustian. Alternative antiretroviral monitoring strategies for HIV-infected patients in east Africa: Opportunities to save more lives? *Journal of International AIDS Society*, 14(30):doi: 10.1186/1758–2652–14–38, 2011.

M.E. Brandt and G. Chen. Feedback control of a biodynamical model of HIV-1. *IEEE Transactions on Biomedical Engineering*, 48(7):754–759, 2001.

D.B. Brown, J.E. Smith, and P. Sun. Information relaxations and duality in stochastic dynamic programs. *Operations Research*, 58(4):785–801, 2010.

CIA. The World Factbook, 2010. Available from http://www.umsl.edu/services/govdocs/wofact2008/index.html, information accessed on 29 Janurary 2013.

A.L. Ciaranello, G.R. Seage, K.A. Freedberg, M.C. Weinstein, S. Lockman, and R. Walensky. Antiretroviral drugs for preventing mother-to-child transmission of HIV in Sub-Saharan Africa: Balancing efficacy and infant toxicity. *AIDS*, 22(17):2359–2369, 2008.

M.S. Cohen and C.L. Gay. Treatment to prevent transmission of HIV-1. *Clinical Infectious Diseases*, 50(Supplement 3):S85–S95, 2010.

D. de Farias and B. Van Roy. On constraint sampling in the linear programming approach to approximate dynamic programming. *Mathematics of Operations Research*, 29(3):462–478, 2004.

P.J. Dodd, G.P. Garnett, and T.B. Hallett. Examining the promise of HIV elimination by test and treat in hyper-endemic settings. *AIDS*, 25(5):729–735, 2010.

J.W. Eaton, T.B. Hallett, and G.P. Garnett. Concurrent sexual partnerships and primary HIV infection: A critical interaction. *AIDS and Behavior*, 15(4):687–692, 2011.

A. Erdelyi and H. Topaloglu. Computing protection level policies for dynamic capacity allocation problems by using stochastic approximation methods. *IIE Transactions*, 41(6): 498 – 510, 2009.

V. Farias, D. Saure, and G. Weintraub. An approximate dynamic programming approach to solving dynamic oligopoly models. To appear in *The RAND Journal of Economics*, 2011.

Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection, 2010. Available from http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates.

C. Fraser, T.D. Hollingsworth, R. Chapman, F. de Wolf, and W.P. Hanage. Variation in HIV-1 set-point viral load: Epidemiological analysis and an evolutionary hypothesis. *Proceedings of the National Academy of Sciences of the USA*, 104(44):17441–17446, 2007.

G.P. Garnett and R.M. Anderson. Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations. *IMA Journal of Mathematics Applied in Medicine and Biology*, 11(3):161–192, 1994.

G.P. Garnett and R.M. Anderson. Sexually transmitted diseases and sexual behavior: Insights from mathematical models. *The Journal of Infectious Disease*, 174(Supplement 2): 150–160, 1996.

P.P. Glasziou, R.J. Simes, and R.D. Gelber. Quality adjusted survival analysis. *Statistics in Medicine*, 9(11):1259–1276, 1990.

R.M. Granich, C.F. Gilks, C. Dye, K.M. De Cock, and B.G. Williams. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: A mathematical model. *The Lancet*, 373(9657):345–353, 2009.

M. Harrington and C.J. Carpenter. Hit HIV hard, but only when necessary. *The Lancet*, 355(9221):2147–2152, 2000.

D.D. Ho. Time to hit HIV, early and hard. *New England Journal of Medicine*, 333(7): 450–451, 1995.

S.D. Holmberg, F.J. Palella, K.A. Lichtenstein, and D.V. Havlir. The case for earlier treatment of HIV infection. *Clinical Infectious Diseases*, 39:1699–1704, 2004.

A.M. Jeffrey, X. Xia, and I.K. Craig. When to initiate HIV therapy: A control theoretic approach. *IEEE Transactions on Biomedical Engineering*, 50(11):1213–1220, 2003.

V.A. Johnson, V. Calvez, H.F. Gnthard, R. Paredes, D. Pillay, R.W. Shafer, A. Wensing, and D.D. Richman. Cost-effectiveness of HIV screening in STD clinics, emergency departments, and inpatient units: A model-based analysis. *Top HIV Med*, 18(5):156–163, 2010.

Joint United Nations Programme on HIV/AIDS. UNAIDS report on the global AIDS epidemic. Available at http://www.unaids.org/en/, 2010.

D. Kirschner, S. Lenhart, and S. Serbin. Optimal control of the chemotherapy of HIV. *Journal of Mathematical Biology*, 35:775–792, 1997.

G. Koole and A. Mandelbaum. Queueing models of call centers: An introduction. *Annals of Operations Research*, 113(1-4):41–59, 2002.

M. Kretzschmar and M. Morris. Measures of concurrency in networks and the spread of infectious disease. *Management Science*, 133(2):165–195, 1996.

H.C. Lane and J.D. Neaton. When to start therapy for HIV infection: A swinging pendulum in search of data. *Annals of Internal Medicine*, 138(8):680–681, 2003.

S.D. Lawn, M.E. Torok, and R. Wood. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. *Current Opinion in Infectious Diseases*, 24(1): 34–42, 2011.

C.P. Lee, G.M. Chertow, and S.A. Zenios. Optimal initiation and management of dialysis therapy. *Operations Research*, 56(6):1428–1449, 2008.

A.C. Lepri, A.N. Phillips, A. d'Arminio Monforte, F. Castelli, A. Antinori, A. de Luca, P. Pezzotti, F. Alberici, A. Cargnel, P. Grima, R. Piscopo, T. Prestileo, G. Scalise, M. Vigevani, and M. Moroni. When to start highly active antiretroviral therapy in chronically HIV-infected patients: Evidence from the ICONA study. *AIDS*, 15(8):983–990, 2001.

J.D.C. Little. A proof for the queuing formula: $l = \lambda w$. *Operations Research*, 9(3):383–387, 1961.

E.F. Long, M.L. Brandeau, C.M. Galvin, T. Vinichenko, S.P. Tole, A. Schwartz, G.D. Sanders, and D.K. Owens. Effectiveness and cost-effectiveness of strategies to expand antiretroviral therapy in St. Petersburg, Russia. *AIDS*, 20(17):2207–2215, 2006.

M. Maxwell, M. Restrepo, S.G. Henderson, and H. Topaloglu. Approximate dynamic programming for ambulance redeployment. *INFORMS Journal on Computing*, 22(2):266–281, 2009.

D. Mollison. *Epidemic Models: Their Structure and Relation to Data*. Cambridge University Press, 1995.

D.C. Montgomery, G.C. Runger, and N.F. Hubele. *Engineering Statistics*. Wiley, Hoboken, New Jersey, 2003.

R. Nelson. *Probability, Stochastic Processes, and Queueing Theory: The Mathematics of Computer Performance Modeling*. Springer, 1995.

F.J. Palella, M. Deloria-Knoll, J.S. Chmiel, A.C. Moorman, A.E. Wood, K.C. Greenberg, and S.D. Holmberg. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Annals of Internal Medicine*, 138(8):620–626, 2003.

F.J. Palella Jr., K.M. Delaney, A.C. Moorman, M.O. Loveless, J. Fuhrer, G.A. Satten, D.J. Aschman, S.D. Holmberg, and the HIV Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *New England Journal of Medicine*, 338(13):853–860, 1998.

J. Patrick, M. Puterman, and M. Queyranne. Dynamic multi-priority patient scheduling for a diagnostic resource. *Operations Research*, 56(6):1507–1525, 2008.

A.N. Phillips, A.C. Lepri, F. Lampe, M. Johnson, and C.A. Sabin. When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. *AIDS*, 17(3):1863–1869, 2003.

M. Pujades-Rodriguez, D. OBrien, P. Humblet, and A. Calmy. Second-line antiretroviral therapy in resource-limited settings: The experience of Medecins Sans Frontieres. *AIDS*, 22(11):1305–1312, 2008.

M.L. Puterman. *Markov Decision Processes*. John Wiley and Sons, New York, New York, 1994.

S.M. Shechter, M.D. Bailey, A.J. Schaefer, and M.S. Roberts. The optimal time to initiate HIV therapy under ordered health states. *Operations Research*, 56(1):20–33, 2008.

M. Shernoff and R.A. Smith. HIV treatments: A history of scientific advance, 2001. Retrieved April 26, 2011, www.thebody.com/bp/jul01/treatments.html.

N. Siegfried, O.A. Uthman, and G.W. Rutherford. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. *Cochrane database of systematic reviews*, 3:doi: 10.1002/14651858, 2010.

T.R. Sterling, R.E. Chaisson, and R.D. Moore. Initiation of highly active antiretroviral therapy at CD4 T lymphocyte counts of >350 cells/mm^3: Disease progression, treatment durability, and drug toxicity. *Clinical Infectious Diseases*, 36(6):812–815, 2003.

G.J. Stine. *AIDS Update, 2003: An Annual Overview of Acquired Immune Deficiency Syndrome*. Prentice Hall, Upper Saddle River, New Jersey, 2003.

M.S. Sulkowski, D.L. Thomas, R.E. Chaisson, and R.D. Moore. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatits C or B virus infection. *JAMA*, 283(1):74–80, 2000.

UNAIDS. Unaids report on the global AIDS epidemic, 2010. Retrieved November 7, 2012, http://www.unaids.org/globalreport/Global_report.htm.

UNAIDS. AIDS dependency crisis: Sourcing African solutions, 2012. Available from http://www.unaids.org/en/resources/publications/unaidspublications/2012/.

United States Department of Health and Services. A guide to primary care of people with HIV/AIDS, 2004. Retrieved November 7, 2012, ftp://ftp.hrsa.gov/hab/PCGchap5.pdf.

J.X. Velasco-Hernandez, H.B. Gershengorn, and S.M. Blower. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? *AIDS*, 2(8):487–493, 2002.

B.G. Wagner, J.S. Kahn, and S. Blower. Should we try to eliminate HIV epidemics by using a test and treat strategy? *AIDS*, 24(5):755–756, 2010.

R.P. Walensky, L.L. Wolf, R. Wood, M.O. Fofana, K.A. Freedberg, N.A. Martinson, A.D. Paltiel, X. Anglaret, M.C. Weinstein, and E. Losina. When to start antiretroviral therapy in resource-limited settings. *Annals of Internal Medicine*, 48(3):178–185, 2009.

C.H. Watts and R.M. May. The influence of concurrent partnerships on the dynamics of HIV/AIDS. *Mathematical Biosciences*, 108(1):89–104, 1992.

L.M. Wein, S.A. Zenios, and M.A. Nowak. Dynamic multidrug therapies for HIV: A control theoretic approach. *Journal of Theoretical Biology*, 185(1):15–29, 1997.

WHO. HIV/AIDS statistics: World Health Organization, 2010. Available from http://apps.who.int/globalatlas/default.asp.

WHO. The global report for research on infectious diseases of poverty, 2012. Available from http://whqlibdoc.who.int/publications/2012/9789241564489eng.pdf.

World Bank. Life expectancy at birth, total (years), 2010. Available from http://data.worldbank.org/indicator/SP.DYN.LE00.IN/countries/ZF?display=graph, information accessed on 20 March 2012.

G.S. Zaric and M.L. Brandeau. Optimal investment in a portfolio of HIV prevention programs. *Medical Decision Making*, 21(5):391–408, 2001.